BACHELOR'S THESIS

Degree in Mathematics

Title: Synchronization in populations of neurons

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Advisors: Toni Guillamon and Alberto Pérez

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Als meus pares i germà, per tota la paciència que han arribat a tenir amb mi.

Abstract

The main goal of this thesis is to initiate into modeling neurons and their networks. For this purpose, we use basic reduced (2D) models, mainly the so-called FitzHugh-Nagumo model which allows analytical computations at the single cell level. At the network level, the basic models allow to understand the coupling mechanisms in a qualitative way, which are complemented with the use of numerical tools. We apply this theory to a specific problem consisting in a network of FitzHugh-Nagumo cells coupled all-to-all. In this network, we adapt a proof given by J. Rubin and D. Terman in [5], to study a particular case of synchrony where all cells are assumed to oscillate together; we are able to give (in an ideal case) both a theoretical constraint for the relative position of the initial value of each cell and for the coupling strength between pairs of cells in order to obtain such a synchrony configuration. Furthermore, we present analytical simulations with N cells to validate these theoretical constraints.

Contents

1 Introduction

MATHEMATICS is one of the most complex sciences that I know. The moment that I had to choose about my thesis, I really did not know what to do, until I decided that it would be interesting to do a mathematical study in the neuroscience world. The actual goal that I have for this thesis is to discover how I can apply all the knowledge I have acquired during these years of the degree to some concepts of neuroscience.

The first step of this thesis will be the biological study of the neurons, how they are composed, how they act, and the way to model their behavior. Apparently, it seems really difficult for me, but with previous knowledge I have acquired during the degree, and using some already proposed models, I will try to study analytically their properties and find my own conclusions.

In this Degree Thesis, I take advantage of neuron models that already been studied. From each model I am going to study how they are created, how they define the behavior of a single neuron and finally how they define a network of coupled neurons. The first model I am going to present is the Hodgkin-Huxley, one of the most specific models but also one of the most complex. Hence, from that one, I am going to propose some reductions. The first one is going to be the model of Rubin-Terman and the second one the FitzHugh-Nagumo model. From the first reduction, we are going to take a study of particular synchronization patterns that we call *snakes* which allow to see the whole behavior of the

network, and from it I am going to try to reply the study to the FitzHugh-Nagumo model.

During the thesis, it is possible to find three different studies: First of all, the bibliographical part. It is essential to understand all the new concepts and situate the project. The second one is the graphical part. Using the programming language *python*, I am going to show all the results in a more visual way. The majority of them are going to be in a less exact way, but they will be useful to see if the analytic study follows the right path. Finally the most analytic part. It will conform the mathematical study of different concepts in the model such as equilibrium points, stability and Hopf bifurcation. In the third part, I am going to adapt the proof of existence of snakes of synchrony from the Rubin-Terman model to the FitzHugh-Nagumo model.

2

Fundamentals of the neuron

2.1 The structure of a neuron

A neuron is a cell of the nervous system that transmits a signal (*bioelectrical impulse*) and allows the communication and processing of information from the brain throughout the body.

Neurons have different parts: the soma, the dendrites and the axon. The interior of the neuron is separated from the exterior by the neuronal membrane.

Next, we review key particularities of the main parts of the neuron:

- *Soma*: It is the central part of the neuron with an spherical appearance. The average size of a cellular body of a neuron is about $20\mu m$ of diameter. The acqueous fluid inside the cell receives the name of *cytosol* and is a rich solution of potassium. The membrane, which has approximately $5nm$ of width, separates the interior with the exterior of the cell. Inside the soma, there exist different structures which all together receive the name of *organelles*. The most important organelles are the nucleus, the rough endoplasmic reticulum, smooth endoplasmic reticulum, Golgi Apparatus and mitochondria. All this material inside the cell membrane, without the nucleus, is

called the *cytoplasm*. The nucleus is an spherical cell, in the center of the soma, and it contains the chromosomes which have the hereditary material, the DNA, that it is the same in each neuron.

- *Axon*: It is the main conducting unit of the neuron. It is the largest extension of the soma and it begins in a place called *axon hillock* and gets thinner until forming the initial segment of the axon. The axon has two very specific characteristics which makes it very different from the soma:

  1. Axons can have a variable length, from $1mm$ to $1m$. In fact, an axon that is originated in an specific neuron and from there, goes to other places, is called *efferent*, while the axon which conducts the impulses to the cellular body of a neuron is called *afferent*.
  2. The length of an axon can be very changeable and it is an important fact, because the speed of an electric signal that goes through the axon, called the *nervous impulse*, can vary depending on the diameter of the axon. A bigger diameter, a quicker impulse.

  The final part of the axon is called the *axon terminal* or *synaptic buttons*, and usually has the shape of a button. It is the part of the neuron where the axon gets in contact with other neurons and transmits the information. This contact point is called *synapse*.

- *Synapse*: It is the place where the transmission of information from a neuron to another happens. It has two phases: the *presynaptic* and *postsynaptic* phases. The presynaptic phase in general takes place in the axon terminal, while the postsynaptic phase can be in a dendrite or in the soma of another neuron. The space between the presynaptic and postsynaptic membrane receives the name of *synaptic cleft*, and the transmission of information in the synapsis between neurons is called *synaptic transmission*. The majority of the information is seen as an electric impulse through the axon, which becomes a chemical signal that goes across the synaptic cleft. In the postsynaptic membrane, this chemical signal becomes an electrical signal again. This chemical signal is called *neurotransmitter* and is kept and liberated by synaptic vesicles inside the terminal. As we are going to study later, different types of neurons use different neurotransmitters.

- *Dendrites*: It is the part of the neuron which looks like the branches of a tree whey they extend from the soma. The dendrites of a neuron can adopt a huge variety of shapes and sizes and this is used to classify different groups of neurons. Each dendrite is covered by thousands of synapses. In the dendritic membrane there are located lots of molecules of specialized proteins called *receptors* which detect the

neurotransmitters in the synaptic cleft. As we have said, we can classify the neurons depending on different aspects:

- Classification depending on the number of dendrites: unipolar (one dendrite), bipolar (two dendrites), multipolar (three or more dendrites). The majority of the neurons in the brain are multipolar.
- Classification depending on the structure of dendrites: pyramidal cells (pyramidal shape) and stellate cells (stellar shaped).
- Classification depending on the connections: primary sensorial neurons (neurons with dendrites in the sensorial surfaces of the organism), motor neurons (neurons with axons which form synapses with the muscles and order the movements), interneurons (neurons which only form connections with other neurons).
- Classification depending on the axon length: Type I Golgi cells (with long axons) and Type II Golgi cells (with short axons).
- Classification based on the neurotransmitters: it is the only kind of classification which does not depend on the morphology of the neuron and it has been possible thanks to more recent methods.

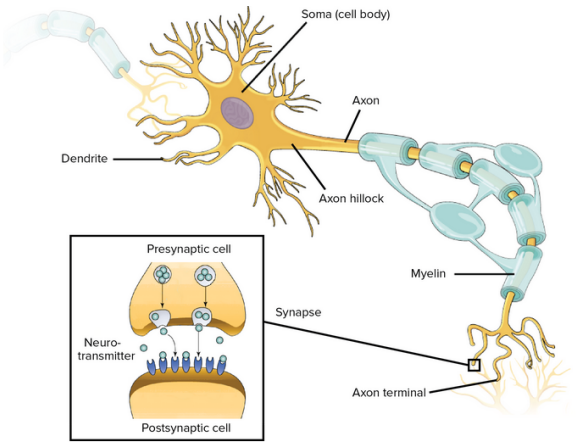

Figure 2.1: The most important parts of the neuron. From [1].

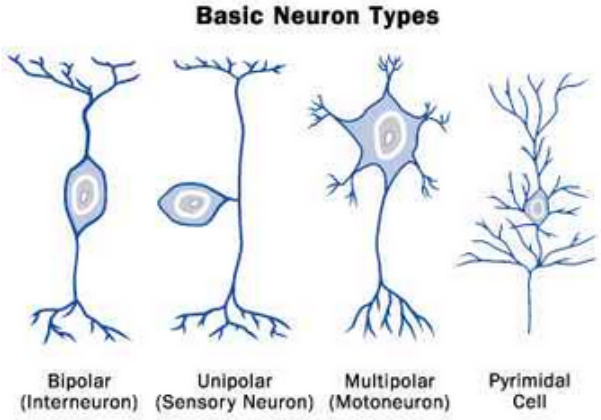

Figure 2.2: Some of the different types of neurons. From [2].

2.2 Neuronal electrical activity

2.2.1 Interaction in the neuron

Inside an organism, there are electrically charged particles, called *ions*. The most important ones in the nervous system are: potassium ions (K^+), sodium ions (Na^+) and chloride ions (Cl^-); while the first ones are found mainly in the intercellular medium, the others are in the extracellular. As we can see, the sodium and potassium ions are positively charged whereas the chloride ions are negatively charged, and it is well known that those differences on the charge cause that two ions with the same charge repell each other while opposite charges induce attraction.

Another important concept are the *ionic channels*, which are protein membranes that allow the ions to move through them. Some of them just allow one kind of ion to pass through them, but others allow all kinds of ions to pas together with no discrimination. There exist two kinds of channels depending on the stimulus which determines its opening. The most important ones are the Voltage-gated Channels, they open depending on the voltage amount.

There exist different kinds of currents: an *inward current* is caused when a positive charged ion (such as Na^+) enters the cell. This fact causes an increase of the *membrane potential*, which is the difference of the ion charge between both sides of the membrane: $V_M = V_{in} - V_{out}$, so that $V_M \to 60mV$. We call it a *depolarization*, and can also be said that the cell is being *depolarized*. On contrary, an *outward current* is caused when a positive charged ion (such as K^+) leaves the cell, or when a negative charged ion

(such as Cl^-) enters the cell. In this case, it is said that the cell becomes *hyperpolarized*. At this point we can define the *permeability* of a membrane to a particular ion, which depends on the number of open channels that are selective for that ion. In fact, neurons at rest are permeable to Na^+, Cl^- and K^+ ions, where the two first move into the cell and the last one outward. Using previous concepts, we can say that the influx of Na^+ ions depolarizes the cell whereas K^+ and Cl^- ions have an opposite effect.

2.2.2 The resting state and the action potential

It exists another parameter that can be found in all alive cells called the *resting potential* V_R, which is the potential across the membrane when a cell is at rest. In the case of neurons, it has been found that $V_R \simeq 70mV$.

In a cell, when gated channels open and allow Na^+, and Cl^- ions to diffuse into the cell and K^+ ions to diffuse outwards, it appears an *action potential*. It has to be noticed that the ions through the cell membrane depend on the conductance of the channels which correspond to its permeability on each ion. Therefore the amount of ions across the channels depends both on the number of channels and their openings.

2.2.3 The Nernst equation

The *reversal potential* of *an specific ion Nernst equilibrium* is the membrane potential of this ion at which it is in equilibrium across the membrane. But this equilibrium is not reached only by the diffusion of ions until the difference from each side is zero, because the separation of positive and negative charges across the cell membrane creates an electric field. If we take, for example K^+ ions, we can calculate the K^+ Nernst potential as:

$$E_k = -\frac{RT}{zF} \ln \frac{[K^+]_{in}}{[K^+]_{out}},$$

where the parameters are:

- R: Boltzmann constant.
- T: absolute temperature calculated in Kelvin degrees.
- z: valence of K^+.
- F: Faraday's constant.
- $[K^+]_{in/out}$: concentration of K^+ ions inside/outside the membrane.

Due to the fact that when the cell is at rest there are more opened K^+ and Cl^- channels than those of Na^+, the cell resting potential can be first determined by K^+ and Cl^- Nernst potential.

At this point, by making a generalization of the Nernst equation assuming that the membrane is permeable to more than one ion, we get the Goldman-Hodgkin-Katz equation. It determines the resting potential at which the electrical and chemical forces are equal. However to arrive to this equation, we have to make some previous calculations The first step is to calculate the *diffusive flux* and the *electrical drift* with the following variables and parameters:

- $[C](x)$: concentration of an specific ion C at a point x.
- $V(x)$: potential at point x across the membrane.
- D: diffusion constant which depends on the size of the molecule and the medium in which it is diffusing. The typical value used for Na^+, K^+ and Cl^- is 2,5 x 10^{-6} cm^2/s.
- $E \equiv -\frac{dV}{dx}$ volts/cm.
- μ: mobility in cm^2/volts s.

Using the Flick's law of diffusion, we get the diffusive flux with molecules/cm^2 s:

$$J_{diff} = -D\frac{\partial[C]}{\partial x}. \tag{2.1}$$

With Ohm's law, the electrical drift equation is:

$$J_{drift} = -\mu z[C]\frac{\partial V}{\partial x}. \tag{2.2}$$

With this equation, it is easy to see that the diffusive flux and the electrical drift have the same direction and the higher concentration we get, the greater drift we obtain.
The second step is calculating the total flux across the membrane.

$$J_{total} = J_{diff} + J_{drift} = -D\frac{\partial[C]}{\partial x} - \mu z[C]\frac{\partial V}{\partial x}. \tag{2.3}$$

Taking the Einstein's relation: $D = \frac{kT}{q}\mu$, where k is the Boltzmann's constant (in J/K), T the absolute temperature and q the charge (in Coulombs), we get the expression in terms of the number of individual molecules:

$$J_{total} = -\frac{\mu kT}{q}\frac{\partial[C]}{\partial x} - \mu z[C]\frac{\partial V}{\partial x}. \tag{2.4}$$

The problem is that we want to express it in terms of the molar equivalence, and the best way to get it is first dividing the expression by the Avogadro's number and then introducing the fraction $\frac{RT}{F}$, where R is the ideal gas constant and F is the Faraday's constant. By making these calculations we obtain the expression of the current flux:

$$I = -\left(uzRT\frac{\partial[C]}{\partial x} + uz^2F[C]\frac{\partial V}{\partial x}\right). \tag{2.5}$$

It is calculated in amperes/cm^2 and it is called the *Nernst-Planck equation*, where u is the molar mobility, in μ/N_A.
From there, we arrive to the equilibrium potential:

$$V_{eq} = V_{in} - V_{out} = -\frac{RT}{zF}\ln\frac{[C]_{in}}{[C]_{out}}. \tag{2.6}$$

Moreover, to arrive to the main purpose of this section, we equal to zero the current flux ($I = 0$) and using the right formula, we obtain the Nernst equation:

$$uzRT\frac{\partial[C]}{\partial x} + uz^2F[C]\frac{\partial V}{\partial x} = 0. \tag{2.7}$$

2.2.4 The Goldman-Hodgkin-Katz equation

As we have seen, the Nernst-Planck equation follows the property of the movement of charged ions in an aqueous media, but in some cell membranes there can be energy barriers that make that the Nernst-Planck equation is not satisfied. For this reason, we are going to study a more complex model. However, it is interesting considering first some simplifications to describe the equation:

1. The electric field across the lipid membrane is constant, so $E = \dfrac{-V_M}{l} \Rightarrow \dfrac{\partial V}{\partial x} = \dfrac{V_M}{l}$.
2. The Nernst-Planck equation holds within the membrane.
3. The ions move all independently.

Recall the variables:

- V_M: total potential across the membrane of width l.
- $V(x)$: potential at point x across the membrane.

At this point, we consider the new variables and parameters:

- u^*: to express the mobility of ions within the membrane.
- β: the ratio of the ion solubility (always within the membrane) in the aqueous solution.
- $[C]$: aqueous concentration.
- $\beta[C]$: membrane concentration.

Then, the Nernst-Planck equation for currents across the membrane, seen as a first order, linear, ordinary differential equation with boundary conditions is:

$$\begin{cases} I = -u^* z^2 F \beta [C] \frac{V_M}{l} - u^* z R T \beta \frac{\partial [C]}{\partial x} \\ C(0) = [C]_{in} \\ C(l) = [C]_{out}. \end{cases} \tag{2.8}$$

Despite the fact that we do not know the value of l it is always possible to choose an specific one to find the solution:

$$I = \frac{u^* z^2 F V_M \beta}{l} \left(\frac{[C]_{out} e^{-\xi} - [C]_{in}}{e^{-\xi} - 1} \right), \tag{2.9}$$

where $\xi \equiv \frac{z V_M F}{RT}$, and adding a new variable $P \equiv \frac{\beta u^* RT}{lF}$ we obtain the solution equation of a current due to a single ionic species, called the *Constant field equation.*

$$I = P z F \xi \left(\frac{[C]_{out} e^{-\xi} - [C]_{in}}{e^{-\xi} - 1} \right). \tag{2.10}$$

It is important to remember that we could be facing another case, having more than one single ionic specie. In that case, to get the total current is as simple as making the sum of individual currents, as follows: supposing that we have K^+, Na^+ and Cl^- ions with respective currents I_K, I_{Na} and I_{Cl}, the total current will be $I = I_K + I_{Na} + I_{Cl}$ and if we are in equilibrium, the current will be $I = I_K + I_{Na} + I_{Cl} = 0$. Using again the Nernst potential, it is possible to calculate the potential at which we have equilibrium:

$$V_M = \frac{RT}{F} \ln \frac{P_K [K^+]_{out} + P_{Na} [Na^+]_{out} + P_{Cl} [Cl^-]_{in}}{P_K [K^+]_{in} + P_{Na} [Na^+]_{in} + P_{Cl} [Cl^-]_{out}}, \tag{2.11}$$

where P_m expresses the permeability to an specific ion m. The last equation is what we were looking for, the *Goldman-Hodgkin-Katz equation.*

2.3 The electrical analogue

2.3.1 Equivalent circuits

It is known that cells have electrical properties, which come from the ionic species that can be found moving through the membrane. More specifically and related to what we have studied until now, there is a current flow which depends on the permeabilities of ion channels and the concentration gradients situated in the cell membranes.

Until now, we have only studied the cell and we have made all the calculations supposing we are in an steady-state environment, when the behavior of the system remains unchanged in time, but in any case we have studied how can change the membrane potential if we have variations on the permeability of the membrane. To study that, the most common and useful thing which has been used in many cases is describing the behaviour of the membrane potential as an equivalent circuit linking:

- Conductors or resistors $\longleftrightarrow$ Ion channels.
- Batteries $\longleftrightarrow$ Concentration gradient of the ions.
- Capacitors $\longleftrightarrow$Ability of the membrane to store charge.

Let us define some remarkable variables and parameters to keep going in this study.

- q: total charge.
- C_M: membrane capacitance (we take it as a constant).
- c_M: specific membrane capacitance.
- I_{cap}: total capacitance current.
- i_{cap}: specific capacitance current, which gives the capacitance current per unit area.

It is possible to express some relations between these variables: first of all, between store charge and potential we have the relation $q = C_M V_M$. Then the total capacitance depends on the total area of the medium: larger neurons have larger total capacitance. For the membrane capacitance: $C_M = c_M \times$ "total surface are of a cell". In fact, for most cell membranes, $c_M \simeq 1\mu F/cm^2$. Finally the specific capacitance current: $i_{cap} = c_M \frac{dV_M}{dt}$
To make the process easier to understand, let us suppose that we are in a cell where there are only K^+ channels. In this case, the equivalent circuit will be like:

- Lipid bilayer $\longleftrightarrow$ Capacitor, which is the place where the charge is stored and then it releases it in form of current.
- K^+ channels $\longleftrightarrow$ Conductors in series with a battery.

If we define the conductance of a single K^+ channel as $\hat{g}_K$ and using Ohm's law, we arrive to determine the ion current through this channel as: $\hat{I}_K = \hat{g}_K(V_M - E_K)$, where E_K is the potential generated by the battery, and its value is given by the Nernst equation, and the factor $(V_M - E_K)$ is the driving force.

Defining N_K as the number of K^+ channels per unit area of membrane, we determine the specific membrane conductance: $g_K = N_K \times \hat{g}_K(s/cm^2)$, and the specific membrane resistance: $r_K = 1/g_K(\Omega cm^2)$.
As the Nernst potential depends only on the concentration gradient of K^+ and not on the number of channels of it, its current per unit area is expressed by:

$$I_K = g_K(V_M - E_K) = \frac{V_M - E_K}{r_K}. \tag{2.12}$$

Using the Kirchoff's current law which says that the total current into a cell must have total sum zero, we get the differential equation for the membrane potential, which can be written in two ways:

1. $0 = i_{cap} + I_K = c_M \dfrac{dV_M}{dt} + \dfrac{V_M - E_K}{r_K}$.
2. $c_M \dfrac{dV_M}{dt} = -\dfrac{V_M - E_K}{r_K} = -g_K(V_M - E_K)$.

We could also have a case where the equivalent circuit is made with three parallel conductances and a current source $I(t)$. In this case the capacitance current per unit area does not change, but it appears a new variable called the *ionic current per unit area*, and it is expressed as: $i_{ion} = -g_{Cl}(V_M - E_{Cl}) - g_{Na}(V_M - E_{Na}) - g_K(V_M - E_K)$.
By making some calculations and adding as new variables A_r as the total surface area of a neuron, E_R the cell's resting potential, and r_M the specific membrane resistance, we obtain:

$$c_M \frac{dV_M}{dt} = -g_{Cl}(V_M - E_{Cl}) - g_{Na}(V_M - E_{Na}) - g_K(V_M - E_K) + \frac{I(t)}{A_r}. \tag{2.13}$$

Equivalently we have:

$$c_M \frac{dV_M}{dt} = -\frac{V_M - E_R}{r_M}, \tag{2.14}$$

$$E_R = (g_{Cl}E_{Cl} + g_K E_K + g_{Na}E_{Na})r_M, \tag{2.15}$$

$$r_M = \frac{1}{g_{Cl} + g_K + g_{Na}}. \tag{2.16}$$

If we face the case in which our cell has a passive membrane, which means that the conductances and currents are constant, our V_M will reach a steady state (V_{SS}):

$$V_{SS} = \frac{g_{Cl}E_{Cl} + g_{Na}E_{Na} + g_K E_K + \frac{I}{A}}{g_{Cl} + g_K + g_{Na}}. \tag{2.17}$$

Once we reach this point, we can affirm that the membrane conductance and permeability are related, but they are not the same thing because the first one depends on both the state of the membrane and the concentration of ions, while the second one depends only on the state of the membrane.

2.3.2 The membrane time constant

Continuing with the study of the electrical field now we take a passive, isopotential cell responding to an applied current. But first, we need to specify some vocabulary:

- *Passive cell*: its electrical properties do not change during signaling. It can not generate an action potential. Many dendrites does not have gated channels so they have passive properties.
- *Isopotential cell*: its membrane potential is uniform at all points. We are going to consider an spherical cell with radius ρ.

As we have taken an isopotential cell, the injected current is distributed uniformly across the surface and the current flow per unit area is given by the formula:

$$I_M(t) = \frac{I(t)}{4\pi\rho^2} = \begin{cases} \frac{I_0}{4\pi\rho^2} & t = 0, \\ 0 & \text{otherwhise.} \end{cases} \tag{2.18}$$

Assuming $E_R = 0$ to make the calculations easier, and using one of the two equivalences of the previous part of the thesis, we obtain:

$$c_M \frac{dV_M}{dt} = -\frac{V_M}{r_M} + I_M(t), \tag{2.19}$$

so if the cell starts at rest, the solution is:

$$V_M(t) = \begin{cases} \frac{r_M I_0}{4\pi\rho^2}\left(1 - e^{-\frac{t}{\tau_M}}\right) & 0 < t < T, \\ V_M(T)e^{-\frac{1}{\tau_M}} & t > T, \end{cases} \tag{2.20}$$

where $\tau_M = c_M r_M$ is the membrane time constant, a value that determines the rate at which the membrane potential decays to rest after the current is turned off.

If we examine the change of membrane potential in response to a step of current, we appreciate that when the current is turned on, the membrane potential asymptotically approaches the steady-state value of $\frac{r_M I_0}{2\pi\rho^2}$. By the equation of the solution we see that the approach is exponential with the time constant τ_M. When we are in the steady-state, the membrane potential satisfies the equality: $I_0 \frac{r_M}{4\pi\rho^2} \equiv I_0 R_{INP}$, where the R_{INP} is the input resistance of the cell. It can be seen in the Figure 2.3.

By the equations, we see that the initial rise in membrane potential is mainly determined by the membrane capacitance. At the initial instant we have the voltage across the resistor and the voltage across the capacitor both equal to zero. That means that there is not current flowing through the resistor and all the current is made by the capacitor. As a consequence, the potential across the capacitor and the membrane potential become more positive, so V_M increases driving the current across the membrane resistance. That causes a lost on the current across the capacitor.

It is not difficult to see that if we are in a case where there is no membrane capacitance, by the equation $V_M = r_M I_M(t)$, the membrane potential jumps to the steady-state potential $(I_0 R_{INP})$ as soon as we turn on the current and jumps back to rest when the current is turned off.

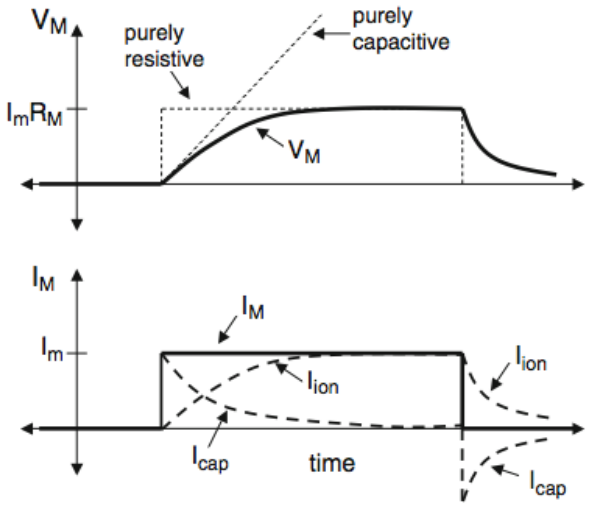

Figure 2.3: Change of membrane potential in response to a step of current. From [4].

2.3.3 The squid action potential

During all the time we have considered the membrane as a passive cable. It is known that linear passive cables need a huge diameter to transmit information at long distances. However we are not facing that problem because many cells have *voltage-gated channels* into the membrane. The function of a channel (made of proteins) is to select which ionic species can go inside the cell through them, but those which are voltage-gated have a different behaviour. Its opening or closure depends on the local potential near the channel. By the opening/closure of the channels, an action potential in generated and then it propagates along the axon.

In 1952, Hodgkin and Huxley were the first to give a description of currents generating the action potential. If we take an isopotential cell, we obtain the membrane potential equation:

$$c_M \frac{\partial V_M}{\partial t} = -g_{Na}(V_M - E_{Na}) - g_K(V_M - E_K) - g_L(V_M - E_L). \tag{2.21}$$

In this equation we have the following variables:

- $I_L = g_L(V_M - E_L)$: leak current. It corresponds to a passive flow of ions through non-gated channels.
- g_L: leak conductance, that in this case is a constant.

As we know, non-gated channels are permeable to K^+ ions, that takes us to see that E_L is close to E_K, and that g_{Na} and g_K can change with time since they correspond to the opening and closing of Na^+ and K^+ channels. As a consequence we have that the amplification of the potential involves changes in the relative conductances of the dominant ionic species.

Let us see how is the behaviour of the action potential. It is graphically expressed in the Figure 2.4.

- *Cell at rest*: Most of the Na^+ channels are closed, so the membrane potential is only determined by the K^+ Nernst potential.

- *Depolarized cell*: The Na^+ channels open and depolarize the cell, that forces even more channels of Na^+ to open, so there are more Na^+ ions and the cell is determined by the Na^+ Nernst potential. It is called the *upstroke* of the action potential.
  We have to notice that Na^+ channels shut down while the depolarization opens K^+

channels and K^+ ions leave the cell.

- *Cell hyperpolarization*: This is caused when the membrane potential moves toward K^+ equilibrium potential. The membrane is called to be in the *refractory period* until the voltage-gated K^+ channels close up again. During this period, the Na^+ ions that are in excess inside the cell are exchanged with excess K^+ ions outside the cell by pumps. The small charge in the concentration of Na^+ ions is needed to generate an action potential.

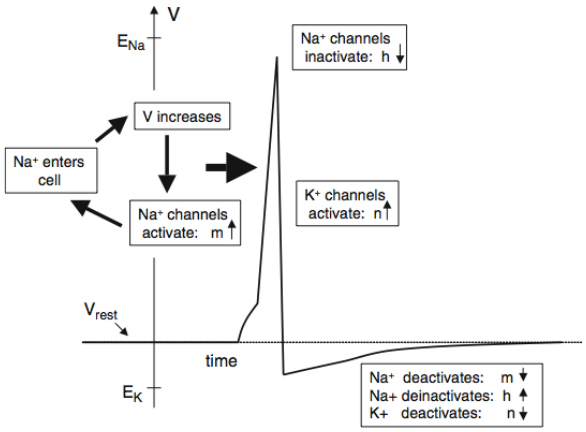

Figure 2.4: Phases of the action potential.From [4].

2.4 Synaptic transmission

In this section we are going to develop and try to explain more specifically how the synaptic transmission works, that is, the transmission of the information between neurons. There are two types of synapses, electrical and chemical, which is the most common one.

2.4.1 Types of synapses

As we have said above, the synapses is the specialized union between neurons. The usual direction of the flux is from the presynaptic cell to the postynaptic cell.

- *Electrical synapses*: It is not the most common synapses but it allows the direct transmission by a ionic flux from a cell to another. They are produced in very specialized places called *interconnection spaces*, where the presynaptic and postynaptic

membranes are only separated by $3nm$ and this small space is full of specialized proteins called *connectors*. As the electrical flux can cross those spaces, it is said that the cells are connected by interconnection spaces which are coupled electrically. The transmission in the electrical synapses is very fast and never fails, so an action potential form the presynaptic neuron always produce an action potential in the postynaptic neuron.

- *Chemical synapses*: In this case, the presynaptic membrane and the postynaptic membrane are separated by a synaptic cleft which has a lenght of $20-50nm$ approximately (10 times the length of the electrical synapses separation). The presynaptic side is usually the terminal of an axon and contains small spheres called *synaptic vesicles* which have neurotransmitters inside. Many axon terminals also have bigger vesicles called *secretory granules*. In the presynaptic space, there are proteins which protrude from the cytoplasm and those are the real places where the release of the neurotransmitters happens. Those zones are called the *active zones*.
  The postynaptic membrane contains the receptors of the neurotransmitters, which transform the chemical intercellular signal to an intracellular signal in the postynaptic cell. The answer can have a high variation, depending on the kind of receptor activated by the neurotransmitters.

2.4.2 First knowledge of the chemical synaptic transmission

To make the chemical synaptic transmition there are some basic necessities. First, a mechanism to synthesise and replace the neurotransmitters in the synaptic vesicles is needed. Second, we require a mechanism that causes that the vesicles pour their contents in the synaptic cleft due to the action potential presynaptic. It is a mechanism to produce an electrical or biochemical answer to the neurotransmitter in the postsynaptic neuron and a mechanism to get the neurotransmitter from the synaptic cleft. Moreover all of this, have to be really quick.

- *Neurotransmitters*: It is known that neurotransmitters can be divided in *amino acids*, *amines* and *peptides*. The first two groups are small organic molecules which contain a nitrogen atom that are stored in the synaptic vesicles, and that then are released by them. The peptidic neurotransmitters are big sized molecules in the secretory granules and also liberated by them.

  The synthesis of neurotransmitters which are ready for their release is needed to have a chemical synaptic transmission. The neurons have specific enzymes which synthesize the neurotransmitters. For the amino acid and amine type neurotransmitters, the enzymes are transported to the terminal by the axon, where

the synthesis of the transmitter is allowed. Once they are synthesized, the synaptic vesicles take those neurotransmitters.

The release of the neurotransmitters is produced by the arrival of an action potential in the axon terminal. The depolarization of the membrane produces the opening of the calcium channels. Then, the vesicles release their content by a process called *exocytosis*: the synaptic vesicle membrane joins with the presynaptic membrane in the active zone and allows the vesicle to pour in the synaptic cleft. These neurotransmitters, once in the cleft, affect the postsynaptic neuron, joining to thousands of specific proteins located in the receptors. We can distinguish two types of receptors: receptors of the ionic channels regulated by a transmitter and receptors associated to the G protein.

- *Ionic channels regulated by transmitters*: These channels are proteins all along the membrane and when a transmitter approaches, the proteins open the membrane making a pore. The functional consequence of this depends on the ions which cross the pore. For example, if the channels are Na^+ permeable, there is a depolarization of the postsynaptic cell from the membrane potential at rest. As this makes the membrane potential to generate an action potential, it is said that this effect is *excitatory*. Otherwise, if the channels are for instance, Cl^- permeable, the effect is hyperpolarizing the postsynaptic cell. As this tends to low the membrane potential, it has an *inhibitory* effect.

- *Receptors associated at the G protein*: It is possible to find slower postsynaptic actions and of larger duration. This kind of action has three phases:

  1. Molecules of the neurotransmitter join to the receptor proteins fixed in the postsynaptic membrane.
  2. Receptor proteins activate small proteic molecules called G proteins that can move freely by the postsynaptic intracellular membrane.
  3. The G proteins activate the effector proteins, which can be ionic channels regulated by the G proteins or enzymes.

Once the neurotransmitters are liberated and have interacted with postsynaptic receptors, they have to go out from the synaptic cleft to allow another synaptic transmission. This occurs thanks to the diffusion of the molecules out the synapses. It can also occur by enzymatic degradation in the synaptic cleft.

3

Modelization of single neurons

THE first modelization of the nervous influx was done by Hodgkin and Huxley in 1952. They described a system of differential equations after experiments they performed in the giant axon of a squid. A few years later, in 1961, R. FitzHugh gave a simplification of the Hodgkin-Huxley model and J. Nagumo proposed an equivalent electrical circuit of this simplified model which, from there on, has been called, the *FitzHugh-Nagumo model*.

From now on in this thesis, the variable of membrane potential is going to be expressed as v instead of V_M to simplify the notation.

3.1 Hodgkin-Huxley Model

First of all, as we have done in the section 2.3.3, we are going to consider the axon of the neuron, a long tube with an exterior membrane with specific properties which permit the propagation of electrical signals. It presents a difference of potential at rest. Our aim is measuring the perturbation of this potential after a chemical or electrical change. This perturbation comes across the axon to transmit the information between the neurons. As we have seen, there are different currents along the axon, but the two principal currents

we are going to consider are: sodium current I_{Na} and potassium current I_K.

What Hodgkin and Huxley proposed was expressing the equations by using the conductances of the sodium channels, g_{Na}, and potassium channels, g_K. The maximum values that these conductances can attain are called maximal conductances, and are denoted by $\hat{g}_{Na}$ and $\hat{g}_K$.Within the model, the changes of conductances depend only on the voltage and on the time while not on the ionic concentration or the current direction.

When an ion crosses the membrane, it appears an electro-chemical gradient caused by the difference of potential and by the equilibrium potential that this ion channel produces. When a channel is closed, ions can not cross through it, but when it is activated, each channel is an open way in which ions can cross the membrane.

The two authors of the model considered that each channel should be composed of independent components, where each one could be open or closed independently from the others. In the potassium case, the channels are composed by four identical components with an opening position with opening probability n. So the probability of having the four (independent) components open is n^4. Let us also consider that the rates from being closed (of probability $1-n$) to being open (of probability n) and viceversa have coefficients α_n and β_n, respectively, both of them depending on the membrane potential. It can be schematized as:

$$1 - n \underset{\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} n.$$

From here it is possible to determine the opening dynamics of the membrane with the equation:

$$\frac{dn}{dt} = \alpha_n(v)(1-n) - \beta_n(v)n = \frac{n_\infty(v) - n}{\tau_n(v)}, \tag{3.1}$$

where the variable n_∞ is the value at equilibrium of n and τ_n is the time constant for approaching this equilibrium. They are defined as:

$$n_\infty(v) := \frac{\alpha_n(v)}{\alpha_n(v) + \beta_n(v)} \text{ and } \tau_n(v) := \frac{1}{\alpha_n(v) + \beta_n(v)}.$$

The last equality of the (3.1) equation, can be seen also as the evolution of the n. The variables $\alpha_n = \alpha_n(v)$, $\beta_n = \beta_n(v)$ and $\tau_n = \tau_n(v)$ all depend on the membrane potential, v. To simplify the notation, we are going to avoid the (v) every time we use these variables.

As a consequence of these calculations, using Ohm's law, it is possible to calculate the quantity of K^+ ions through the membrane, replacing $g_K = n^4\hat{g}_K$ and obtaining:

$$I_K = n^4\hat{g}_K(v - E_K), \tag{3.2}$$

where E_K is the equilibrium potential of K^+ ions. Moreover it is possible to see that, if there is no conductance, ions cannot cross.

In the sodium case, it exists one more state and sodium channels can be in one of these three states: open and active (when the channels are open and allow ions to cross), open and inactive (when the open channels become impermeable to ions) or closed. As in the potassium case, we consider that there are four components to modelize the states. The first three control the opening and closure in an independent way, with probability m of being open, and probability $1-m$ of being closed. The component that controls the activation and inactivation has a probability h of being active and $1-h$ of being inactive. Recall that there is independence among the four components. As with potassium channels, we have the reaction schemes:

$$1-m \underset{\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} m \quad , \quad 1-h \underset{\beta_h}{\overset{\alpha_h}{\rightleftharpoons}} h.$$

From here, we can calculate the amount of Na^+ ions across the membrane, again using Ohm's law:

$$I_{Na} = m^3 h \hat{g}_{Na}(v - E_{Na}). \tag{3.3}$$

Moreover we can define the evolution of m and h in the same way we have done with potassium using the differential equations:

$$\frac{dm}{dt} = \alpha_m(v)(1-m) - \beta_m(v)m = \frac{m_\infty(v) - m}{\tau_m(v)}, \tag{3.4}$$

$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h(v)h = \frac{h_\infty(v) - h}{\tau_h(v)}, \tag{3.5}$$

with the equilibrium values and the time constants:

$$m_\infty(v) = \frac{\alpha_m(v)}{\alpha_m(v) + \beta_m(v)}, \qquad \tau_m(v) = \frac{1}{\alpha_m(v) + \beta_m(v)},$$

$$h_\infty(v) = \frac{\alpha_h(v)}{\alpha_h(v) + \beta_h(v)}, \qquad \tau_h(v) = \frac{1}{\alpha_h(v) + \beta_h(v)}.$$

Actually, the values of $m_\infty(v)$, $n_\infty(v)$ and $h_\infty(v)$ are often expressed as an exponential of the form:

$$\frac{1}{1 + e^{-\dfrac{v - v_h}{v_s}}}, \tag{3.6}$$

where v_s and v_h are constants. Let us see how is the process to obtain it. For example, if we take $m_\infty(v)$ with $\alpha(v) = A_\alpha e^{-B_\alpha v}$ and $\beta(v) = B_\beta e^{-B_\beta v}$:

$$m_\infty(v) = \frac{\alpha(v)}{\alpha(v) + \beta(v)} = \frac{A_\alpha e^{-B_\alpha v}}{A_\alpha e^{-B_\alpha v} + A_\beta e^{-B_\beta v}} = \frac{e^{-B_\alpha v}}{e^{-B_\alpha v} + \frac{A_\beta}{A_\alpha} e^{-B_\beta v}} = \frac{1}{1 + \frac{A_\beta}{A_\alpha} e^{(-B_\beta + B_\alpha)v}} =$$

$$= \frac{1}{1+\frac{A_\beta}{A_\alpha}e^{(-B_\beta+B_\alpha)v}} = \frac{1}{1+e^{\ln\frac{A_\beta}{A_\alpha}}e^{(-B_\beta+B_\alpha)v}} = \frac{1}{1+e^{\ln\frac{A_\beta}{A_\alpha}+(-B_\beta+B_\alpha)v}} =$$

$$= \left(1+\exp\left(-\frac{v-\frac{\ln\frac{A_\beta}{A_\alpha}}{B_\beta-B_\alpha}}{\frac{1}{B_\beta-B_\alpha}}\right)\right)^{-1} \tag{3.7}$$

where $v_h = \dfrac{\ln\frac{A_\beta}{A_\alpha}}{B_\beta - B_\alpha}$ and $v_s = \dfrac{1}{B_\beta - B_\alpha}$.

Until now, we have been doing the analysis of a single ion, however to obtain the resulting model with all the ion channels, it is needed to take the different equations from all the ions. To do that, we are going to use the Kirchhoff's law. From it we get the equality of electrical charges from the equation:

$$I = c_M\frac{dv}{dt} + I_{Na} + I_K + I_L \Longrightarrow -c_M\frac{dv}{dt} = I_{Na} + I_K + I_L - I$$

$$\Longrightarrow -c_M\frac{dv}{dt} = m^3h\hat{g}_{Na}(v-E_{Na}) + n^4\hat{g}_K(v-E_K) + \hat{g}_L(v-E_L) - I. \tag{3.8}$$

Finally we get the model proposed by Hodgkin and Huxley:

$$\begin{cases} c_M\dfrac{dv}{dt} = -m^3h\hat{g}_{Na}(v-E_{Na}) - n^4\hat{g}_K(v-E_K) - \hat{g}_L(v-E_L) + I \\ \dfrac{dn}{dt} = \alpha_n(1-n) - \beta_n n = \dfrac{n_\infty - n}{\tau_n} \\ \dfrac{dm}{dt} = \alpha_m(1-m) - \beta_m m = \dfrac{m_\infty - m}{\tau_m} \\ \dfrac{dh}{dt} = \alpha_h(1-h) - \beta_h h = \dfrac{h_\infty - h}{\tau_h}. \end{cases} \tag{3.9}$$

Once obtained the mathematical model, we are going to interpretate it and understand the dynamic of opening and closure of the ionic channels depending on the voltage. Actually, we are going to study how the action potential (studied more biologically in chapter 2) is created. We can see the solution in Figure 3.1.

The first thing that we can say is that when we depolarize the cell:

- n_∞ and m_∞ increase, whereas h_∞ decreases. That means that K^+ channels are open while Na^+ channels are initially open but inactivated, progressively closing and activating as v increases.

- τ_m is much smaller than τ_n and τ_h. That means that Na^+ channels activate faster than they inactivate or K^+ channels open.

In conclusion, Na^+ conductance leads to a large increase in the Na^+ conductance and is faster than the K^+ conductance. The increase in Na^+ conductance induces a big increase in the Na^+ current. While the cell is near rest, the driving force $(v - E_{Na})$ is large, so:

- The Na^+ current will dominate the equation for the membrane potential.
- v will increase towards the Na^+ Nernst equation. While this happens, m_∞ increases activating even more Na^+ channels.

As v increases toward E_{Na}:

- Na^+ channels inactivate because $h \longrightarrow h_\infty \approx 0$ for large values of v.
- Na^+ driving force $(v - E_{Na})$ decreases.

Both consequences cause the sodium current to turn off. Meanwhile, potassium channels activate because $n \longrightarrow n_\infty \approx 1$ for large values of v and the driving force $(v - E_K)$ becomes very large. This causes that K^+ current dominates and the membrane potential must fall back toward the K^+ Nernst potential, causing what is called *the downstroke of the action potential*. After that, the cell is hyperpolarized with $m_\infty \approx 0$, $n_\infty \approx 0$ and $h_\infty \approx 1$. Then, the variables n, m and h approach their steady-state values and the cell returns to rest.

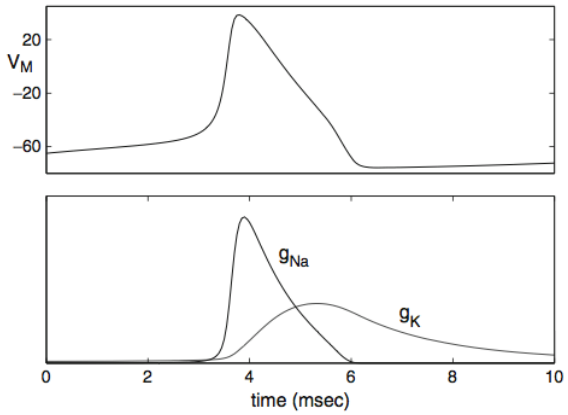

Figure 3.1: The upper image is the solution of the Hodgkin-Huxley equations showing an action potential, the image below shows the time course of conductances of sodium and potassium. From [4].

3.2 Two dimensional reduction of the Hodgkin-Huxley model

Since the Hodgkin-Huxley model was published, there have been a lot of bidimensional reductions proposed. In general, all have a similar structure where it is tried to join the variables which act in similar time scales (v and m by one side, n and h by the other). There are different ways to get these reductions, but there is a generic form which express them all.

3.2.1 Individual cells

For this study we will use the following variables and parameters:

- v: representing the membrane potential of the cell and other variables acting at a similar timescale.
- w: channel gating variable. It represents the channel state that activates or inactivates slower than the other variable.
- ϵ: small positive parameter. It is used in the second equation to equal the time scale in all the system.

This system is a general way to show that the analysis does not depend on the specific form of the equations. Moreover, as neuronal systems are constructed by processes calculated in different timescales, it is important to avoid those differences on the timescales. It is done, by the use of ϵ.

$$\begin{cases} \dfrac{dv}{dt} = f(v,w) \\ \dfrac{dw}{dt} = \epsilon g(v,w). \end{cases} \tag{3.10}$$

Let us make some assumptions, which are also present in most of the reductions:

- The *v-nullcline* (the subset of the plane where $f(v,w) = 0$) defines a cubic-shaped curve.
- w-nullcline($g = 0$) defines a monotone increasing curve.
- $f > 0$ is below ($f < 0$ is above) the v-nullcline.
- $g > 0$ is below ($g < 0$ is above) the w-nullcline.

3.2.2 Singular construction of the Action Potential

Recall the system (3.10) with v, w and ϵ.

We are going to refer to the v-nullcline as the resulting equation of $\frac{dv}{dt} = f(v,w) = 0$, respectively we are going to refer to the w-nullcline to the resulting equation of $\frac{dw}{dt} = \epsilon g(v,w) = 0$. The v-nullcline is going to be approximated as a cubic and the maximum and minimum are going to be located on what is called the right and left knee of the cubic respectively.

What we are really interested in, is to find the intersection point between the nullclines, when $f(v,w) = g(v,w) = 0$. If this intersection point have the two negative eigenvalues of the vector field, it is going to be an stable point. If not, it is going to be an instable point which, under some conditions of the $f(v,w)$ and $g(v,w)$, the Poincar-Bendixson Theorem assures the existence of a periodic orbit or a limit cycle when the point is repulsor (instable with two positive eigenvalues).

Assuming the w-nullcline intersects the cubic at a single point in the middle branch, we can assure that this fixed point is instable so there is a stable periodic orbit. In the image below we have the periodic solution of an action potential and its (v,w)-phase plane:

To give an explanation of this behavior, we are going to use geometric singular perturbation methods. In this case, we have the two timescales: the fast timescale (t) used to describe the solutions on the jumps up and down, and the slow ($\tau = \epsilon t$) which is used during the silent and active phases. We are going to make ϵ tend to 0 to study how are generated the oscillations, but as it is a singular system, this does not assure the existence of a limited cycle for $\epsilon > 0$. In fact, to assure it, there are needed some more explicid theorems. So, when calculating a temporal derivative, we make the change:

$$\tau = \epsilon t \Longrightarrow \frac{dv}{dt} = \epsilon \frac{dv}{d\tau}.$$

Slow timescale: τ. With the time scale change and setting $\epsilon = 0$, the system becomes:

$$\begin{cases} \dfrac{dv}{dt} = f(v,w) \to \epsilon \dfrac{dv}{d\tau} = f(v,w) \to 0 = f(v,w) \\ \dfrac{dw}{dt} = \epsilon g(v,w) \to \dfrac{1}{\epsilon}\dfrac{dw}{dt} = g(v,w) \to \dfrac{dw}{d\tau} = g(v,w). \end{cases} \tag{3.11}$$

As the first equation related to the cubic is equal to zero, the silent and active phases lie in the left and right branches respectively, meanwhile the second equation determines the time evolution of those phases.

Fast timescale: t. If we set $\epsilon = 0$ as we have done in the slow timescale, we obtain:

$$\begin{cases} \dfrac{dv}{dt} = f(v,w) \\ \dfrac{dw}{dt} = 0. \end{cases} \tag{3.12}$$

In that case, the second equation means that during the jumps up and down, the w variable remains constant. During the jump up, w has a constant value and approaches the left knee at the time of $t \to -\infty$. During the jump down, w has another constant value and approaches the right knee at the time of $t \to -\infty$.

The result of what has been studied can be seen in the graphics in Figure 3.2:

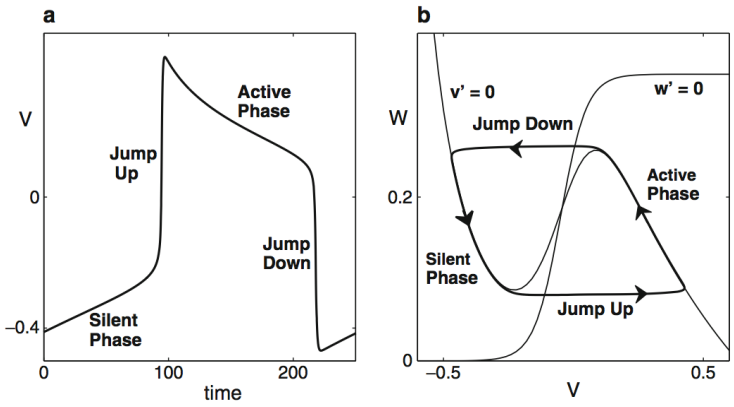

Figure 3.2: Different phases of the action potential and its its phase plane of a single action potential. From [4].

The second important thing of this section is adding a current (inhibitory or excitatory) to the neuron and study how a neuron responds to it. If we are in this context, we write the system:

$$\begin{cases} \dfrac{dv}{dt} = f(v,w) + I(t) \\ \dfrac{dw}{dt} = \epsilon g(v,w). \end{cases} \tag{3.13}$$

We are going to assume that the system is going to be *excitable* (which means that there is a stable equilibrium point close to the bifurcation which gives the limit cycle), if $I(t) = 0$ which means that the v and w-nullclines intersect at a point which is stable, fixed and

located on the left branch of the cubic. If we are not in the excitable case, we can define:

$$I(t) = \begin{cases} I_0 & T_{\text{on}} < t < T_{\text{off}}, \\ 0 & \text{otherwise.} \end{cases} \tag{3.14}$$

where T_{on} is the exact time of turning on the input current and T_{off} is the moment of turning off the current.

It is important to consider the sign of the initial current (I_0) because if it is positive, the injected current is called *depolarizing* and the neuronal response is firing a series of action potentials returning to rest only when the current is turned off, whereas if it is negative it is called *hyper polarizing* and the membrane potential tends to a more negative steady state until the current is turned off, and at this time the neuron may fire a single action potential, called *post inhibitory rebound*. The options are shown graphically in Figure 3.3:

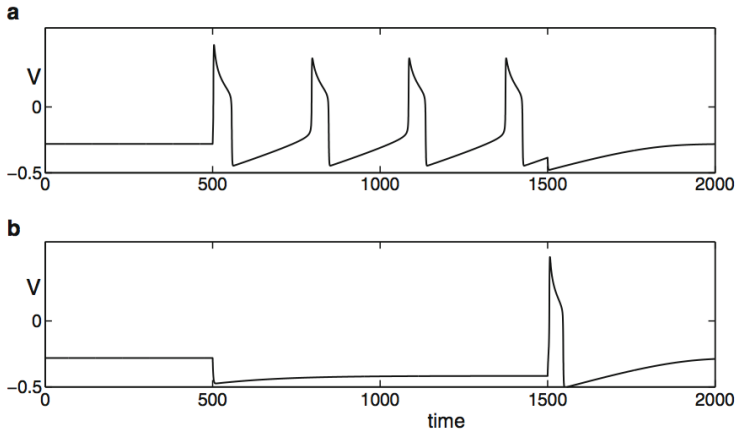

Figure 3.3: Behavior of the neuron after an applied current. In the image (a) is a depolarizing current while in (b) an hyper polarizing current. From [4].

3.3 Resulting simplified models

From all the obtained reductions, we have picked two. By one hand the Rubin and Terman reduction because we are going to inspire by one of their projects. By the other hand, we are going to take the FitzHugh-Nagumo reduction because it is the most used for its simplicity and because we want to apply the Rubin and Terman study to our model.

3.3.1 Rubin Terman model

As observed in [3], J. Rubin and D. Terman defined a mathematical model for a network of neurons in the brain stem. Those neurons are responsible of the inspiratory phase of the respiratory rate. More specifically, they have reduced the activity patterns of a network of heterogenous cells, some are silent while others spike repeatedly. The main objective is to study how the burst frequencies of the bursting cells vary depending on the cell properties and the connections between them. Experimentally they have shown that a coupled network in a region of the brain stem typically behaves as a synchronized bursting oscillator. A previous simulation reflected that individual silent neurons in the specific region of the brain stem can behave as a repeatedly bursting cell by changing some parameters of the model. With this model, our aim is to study the behavior of the network in the same way they have done, but with the FitzHugh-Nagumo model.

Single neuron model

The model of each cell is described by the next system of ordinary differential equations:

$$\begin{cases} v' = f(v,w) + I_{app} + I_{syn} \\ w' = \epsilon g(v,w). \end{cases} \tag{3.15}$$

They define $v = v(t)$ as the membrane potential of the cell, w as the channel state variable, I_{app} as the applied current, $\epsilon > 0$ as a small singular perturbation parameter and I_{syn} as the coupling from other cells.

From the model above and extending it to a more specific one, we find:

$$\begin{cases} c_m v' = -g_{Na} m_\infty(v) w (v - v_{Na}) - g_L(v - v_L) + I_{syn} + I_{app} \\ w' = \dfrac{w_\infty(v) - w}{\tau_w(v)}. \end{cases} \tag{3.16}$$

3.3.2 FitzHugh-Nagumo model

This model allows us to obtain the complete solution and a geometric explanation of the phenomena related to action potentials and its excitability. The main purpose is to reduce the Hodgkin-Huxley model until getting a two-equation system. To get it, we are going to make some assumptions:

- The sodium activation is very fast, so we can do the approximation: $m \approx m_\infty$. That makes possible to see m as a function of v and the differential equation for m is not relevant anymore.

- Experimentally it has been seen: $h_\infty(v) + n_\infty(v) = 0.8$. Hence, we can express the relation $h + an = b$ where a and b are constants. From here, it is possible to determinate the new variable as a linear combination defined as:

$$w = b - h = an \Longrightarrow \frac{dw}{dt} = \frac{s_\infty(v) - w}{\tau_w(v)}.$$

Taking all these simplifications, we get a more reduced system:

$$\begin{cases} \dfrac{dv}{dt} = \dfrac{1}{c_{\mathrm{M}}}\left[m_\infty^3(b-w)\hat{g}_{Na}(E_{Na}-v) + \left(\dfrac{w}{a}\right)^4 \hat{g}_K(E_K - v) + \hat{g}_L(E_L - v) + I \right] \\ \dfrac{dw}{dt} = \dfrac{w_\infty - w}{\tau_w}. \end{cases} \tag{3.17}$$

We will not arrive to the final simplification of the Hodgin-Huxley model only with these arrangements. This system is strongly similar to the Van der Pol oscillator system, with which Richard Fitzhugh was familiarized. Then what he did was adding some terms to a special case of the Van der Pol oscillator, and obtained the resulting polynomial form:

$$\begin{cases} \dfrac{dv}{dt} = v - \dfrac{v^3}{3} - w + I \\ \dfrac{dw}{dt} = \dfrac{1}{\tau}(v + a - bw). \end{cases} \tag{3.18}$$

It is not difficult to see that the v-nullcline can be approximated as a cubic function, while the w-nullcline as a curve. The main purpose of this section is to study the behavior of the (3.18) model that we have obtained, known as the FitzHugh-Nagumo model:

$$\begin{cases} \dfrac{dv}{dt} = f(v,w) = v - \dfrac{v^3}{3} - w + I \\ \dfrac{dw}{dt} = g(v,w) = \dfrac{1}{\tau}(v + a - bw). \end{cases} \tag{3.19}$$

where v is the membrane potential, w is the flux of the ions through the membrane, I is an external applied current and a, b and τ with $\tau > 0$ are the parameters.
To make the analysis we are going to use tools of qualitative theory of ordinary differential equations.

Equilibrium points

To find the equilibrium points, we must solve the system of (3.18) equaled to zero:

$$\begin{cases} \dfrac{dv}{dt} = f(v,w) = 0 \\ \dfrac{dw}{dt} = \epsilon g(v,w) = 0. \end{cases} \tag{3.20}$$

That is,

$$\begin{cases} v - \dfrac{v^3}{3} - w + I = 0 \\ \dfrac{1}{\tau}(v + a - bw) = 0 \end{cases} \implies w = \frac{v+a}{b} \implies v - \frac{v^3}{3} - \frac{v+a}{b} + I = 0$$

$$\implies v^3 - \frac{3(b-1)}{b}v + \frac{3a}{b} - 3I = 0 \implies v^3 + mv + n = 0\ . \tag{3.21}$$

Assuming $b \neq 0$, define the new variables $m := -\dfrac{3(b-1)}{b}, n := \dfrac{3a}{b} - 3I$.

Using the formula of the discriminant for a cubic equation we obtain: $\Delta = -4m^3 - 27n^2$ and we have three options:

- If $\Delta > 0$ there are three real solutions.
- If $\Delta = 0$ there are at least two real equal roots, the third can be or not equal.
- If $\Delta < 0$ there are three solutions, where one of them is real and the other two are complex.

Those solutions are the equilibrium points.

Stability

The Qualitative Theory of Ordinary Differential Equations says that it is needed to study the Jacobian matrix of (f, g) and its behavior when valuated in the equilibrium points.

$$DJ(v,w) = \begin{pmatrix} \dfrac{\partial f(v,w)}{\partial v} & \dfrac{\partial f(v,w)}{\partial w} \\ \dfrac{\partial g(v,w)}{\partial v} & \dfrac{\partial g(v,w)}{\partial w} \end{pmatrix} = \begin{pmatrix} 1 - v^2 & -1 \\ \dfrac{1}{\tau} & -\dfrac{b}{\tau} \end{pmatrix}. \tag{3.22}$$

From this matrix, we have:

- Trace of $DJ(v,w) = -v^2 + 1 - \dfrac{b}{\tau}$.
- Determinant of $DJ(v,w) = -\dfrac{b(1-v^2)}{\tau} + \dfrac{1}{\tau}$.

At this point, it is important to study the sign (positive or negative) of the trace and determinant. However, we have some parameters from which depends on having positive or negative trace and determinant.

It is interesting to study the cases in which we have a change on the sign of the value v. So, making some calculations we obtain:

$$-v^2 + 1 - \frac{b}{\tau} = 0 \Longrightarrow v = \pm\sqrt{1 - \frac{b}{\tau}}. \tag{3.23}$$

As we want real solutions, we take $\tau > b$.
Now we want to determine the solutions of the determinant:

$$0 = -\frac{b(1-v^2)}{\tau} + \frac{1}{\tau}. \tag{3.24}$$

The discriminant of the solution of this equation is $\Delta = -\frac{4b(1-b)}{\tau^2}$ and as we want real values, we need the condition: $b(1-b) < 0$, so $b < 0$ or $b > 1$. From the equations (3.24) we arrive to the values:

$$-\frac{b(1-v^2)}{\tau} + \frac{1}{\tau} = 0 \Longrightarrow v = \pm\sqrt{1 - \frac{1}{b}}. \tag{3.25}$$

It is easy to see that we are facing a case where depending on the parameters, we obtain different solutions.

1. There is a specific case when $b = 0$, in which we obtain an equilibrium point in $E = (-a, -a + \frac{a^3}{3} + I)$ which is an stable point if $|a| > 1$, a center if $|a| = 1$ or an unstable point if $|a| < 1$.

2. There is another case if we take $b \geq \tau$ and $0 < b < 1$, which it has only one stable node.

3. The last case and the most important and complex one is when taking $0 < b < 1$, $\tau \gg 0$ and $\tau \gg b$. We can say for sure that the solution of v is not going to be larger than 1, $v^* \leq 1$. And the resulting table of results is:

v	$-\infty$		$-\sqrt{1-\frac{b}{\tau}}$		$\sqrt{1-\frac{b}{\tau}}$		$+\infty$
Trace of DJ		$-$	0	$+$	0	$-$	
Determinant of DJ		$+$	$\vdots$	$+$	$\vdots$	$+$	
Stability		stable	$\vdots$	instable	$\vdots$	stable	
Element		node	$\vdots$	node	$\vdots$	node	
			minimum		maximum		

From now on, we are going to use the * to express the solution values.

At this point, it is important to take the main equation $f(v, w)$ and see its behavior depending on the other parameter a to finally determinate its properties.

$$v^3 - \frac{3(b-1)}{b}u + \frac{3a}{b} - 3I = 0 \Longrightarrow \frac{a}{b} = I + \frac{b-1}{b}u - \frac{u^3}{3}$$

$$\Longrightarrow a = bI + (b-1)u - \frac{bu^3}{3} = bu - \frac{b}{3}u^3 - u + Ib. \tag{3.26}$$

If we consider a as a value depending on $a(v)$, it is easy to study how it evolves using its derivative: $a' = b - bv^2 + 1 < 0 \ \forall b \in (0, 1)$. As the derivative is negative, we deduce that the function v is decreasing, from $+\infty$ to $a(-1) = -b + \frac{b}{3} + 1 + Ib = -\frac{2b}{3} + 1 + Ib$.

To assure excitability, we are going to make the assumption: $-2 < v \leq -1$, so we can assure that the equilibrium point is not very far from the local minimum of v. Using these values, we can bound the values of a:

$$a(-1) = 1 - \frac{2b}{3} + Ib < a < \frac{2b}{3} + 2 + Ib = a(-2). \tag{3.27}$$

As a conclusion, we obtain the FitzHugh-Nagumo model:

$$\begin{cases} \dfrac{dv}{dt} = v - \dfrac{v^3}{3} - w + I \\ \dfrac{dw}{dt} = \dfrac{1}{\tau}(v + a - bw). \end{cases} \tag{3.28}$$

with the conditions: $0 < b < 1$, $b \ll \tau$ and $1 - \dfrac{2b}{3} + Ib < a < \dfrac{2b}{3} + 2 + Ib$.

Phase plane

At this point, it is interesting to study the phase plane, and to do that, we are going to take some values obtained by experimental studies. Those values for the parameters are:

$\frac{1}{\tau} = 0.08$, $a = 0.7$, $b = 0.8$ and $I = 0$ and the system in (3.28) remains:

$$\begin{cases} \dfrac{dv}{dt} = v - \dfrac{v^3}{3} - w \\ \dfrac{dw}{dt} = 0.08(v + 0.7 - 0.8w) \end{cases} \tag{3.29}$$

With these values, there is an equilibrium point P = (-1.2 , -0.62) obtained equaling the equations to zero as we have done in the system (3.20). The entire graphic is shown in Figure 3.4.

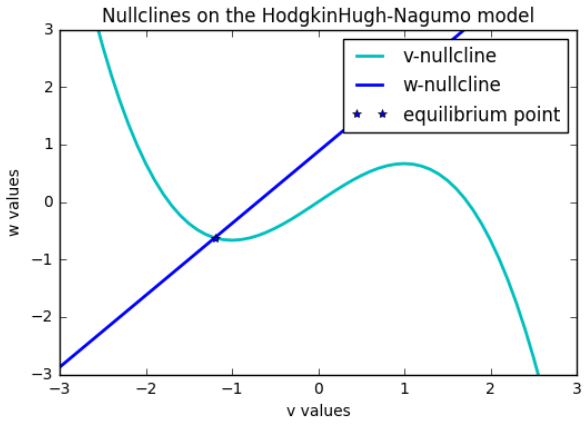

Figure 3.4: Nullclines of the FitzHugh-Nagumo model and the equilibrium point for $I = 0$.

We want it to be excitable, so using what we have studied, the intersection point have to be in the left branch of the cubic, so it is necessary to add as an assumption that the values of $(v(0), w(0))$ have to be on that branch, but not in the stability point, because if they are the same, then they will not evolve and will remain in that point.

Hopf bifurcation

The sistem in which we are working, the mecanisms that generate the periodic orbits are the Hopf bifurcations. This is the main reason why we are going to study what are the Hopf bifurcations and when they are generated in our model. In [5] we can find the following theorem.

Theorem: *If there is a two ordinary differential equation system,*

$$\begin{cases} \dfrac{dv}{dt} = f(v, w, a) \\ \dfrac{dw}{dt} = g(v, w, a) \end{cases}$$

Let us call (v^*, w^*) the equilibrium of the system for every a. If the jacobean matrix of the system evaluated at (v^*, w^*) admits two conjugated imaginary eigenvalues, $\lambda_{1,2}(a) = \alpha(a) \pm i\gamma(a)$ and if there exist a specific $a = a_c$ which

$$\alpha(a_c) = 0,\ \gamma(a_c) \neq 0 \quad \text{and} \quad \frac{\partial \alpha(a)}{\partial a}(a_c) \neq 0,$$

then, a Hopf Bifurcation occurs when the value of the bifurcation parameter a_c and $((v^*, w^*), a_c)$ is a Hopf bifurcation point. Furthermore, we obtain c_1 with:

$$c_1 = \frac{1}{16\gamma(a_c)}\left(-\frac{\partial^2 F}{\partial v^2}\frac{\partial^2 G}{\partial v^2} + \frac{\partial^2 F}{\partial v^2}\frac{\partial^2 F}{\partial v \partial w} - \frac{\partial^2 G}{\partial v^2}\frac{\partial^2 G}{\partial v \partial w} - \frac{\partial^2 G}{\partial w^2}\frac{\partial^2 G}{\partial v \partial w} + \frac{\partial^2 F}{\partial w^2}\frac{\partial^2 F}{\partial v \partial w} + \frac{\partial^2 F}{\partial w^2}\frac{\partial^2 G}{\partial w^2}\right)$$
$$+ \left(\frac{\partial^3 F}{\partial v^3} + \frac{\partial^3 F}{\partial v \partial w^2} + \frac{\partial^3 G}{\partial v^2 \partial w} + \frac{\partial^3 G}{\partial w^3}\right)$$

where F and G are given by the Hassard, Kazarinoff and Wan method.
We can distinguish different cases:

		$c_1 < 0$	$c_1 > 0$
$\frac{\partial \alpha}{\partial a}(a_c) > 0$	$a < a_c$	stable eq. but no periodic orbits	stable eq. and periodic unstable orbits
	$a > a_c$	unstable eq. and stable periodic orbits	unstable eq. but no periodic orbits
$\frac{\partial \alpha}{\partial a}(a_c) < 0$	$a < a_c$	unstable eq. and stable periodic orbits	unstable eq. but no periodic orbits
	$a > a_c$	stable eq. but no periodic orbits	stable eq. and unstable periodic orbits

Hence, to determine the results of our system, we have to calculate the values of: $\frac{\partial \alpha}{\partial a}(a_c)$, a_c (which in our case is going to be $I_\pm$) and c_1. We have the system:

$$\begin{cases} \dfrac{dv}{dt} = v - \dfrac{v^3}{3} - w + I \\ \dfrac{dw}{dt} = \dfrac{1}{\tau}(v + a - bw). \end{cases} \tag{3.30}$$

1. Let us call (v^*, w^*) the equilibrium point. We have previously calculated them in the specific case. To do it, we only needed to follow the same path: equal the two equations to zero, and find the values of v and w.

2. As we want the resulting Jacobian to find the imaginary eigenvalues, we have to linearize the system, and the resulting one is:

$$\begin{cases} \dfrac{dv}{dt} = f(v^*, w^*, I) + \dfrac{\partial f}{\partial v}(v^*, w^*, I)(v - v^*) + \dfrac{\partial f}{\partial w}(v^*, w^*, I)(w - w^*) \\ \dfrac{dw}{dt} = g(v^*, w^*, I) + \dfrac{\partial g}{\partial v}(v^*, w^*, I)(v - v^*) + \dfrac{\partial g}{\partial w}(v^*, w^*, I)(w - w^*), \end{cases}$$

which in our system, we obtain the resulting:

$$\begin{cases} \dfrac{dv}{dt} = (v^* - \dfrac{(v^*)^3}{3} - w^* + I) + (1 - (v^*)^3)(v - v^*) + (-1)(w - w^*) \\ \dfrac{dw}{dt} = \dfrac{1}{\tau}(v^* + a - bw^*) + \dfrac{1}{\tau}(v - v^*) - \dfrac{b}{\tau}(w - w^*). \end{cases} \tag{3.31}$$

3. From the (3.31) equation, we obtain the linearized Jacobian evaluated in (v^*, w^*, I):

$$A = DJ(v^*, w^*, I) = \begin{pmatrix} 1 - (v^*)^2 & -1 \\ \dfrac{1}{\tau} & -\dfrac{b}{\tau} \end{pmatrix}. \tag{3.32}$$

4. Its characteristic polynomial can be calculated with the formula:

$$P_c = \lambda^2 + (-Tr(A))\lambda + Det(A) = 0 \Rightarrow \lambda = \frac{Tr(A) \pm \sqrt{Tr(A)^2 - 4Det(A)}}{2}. \tag{3.33}$$

As we want to have a Hopf bifurcation, it is needed that $\alpha(a_c) = 0$, in our case it means that $Tr(A)$ has to be equal to zero when evaluated in the equilibrium point. So we have that:

$$Tr(A) = (1 - (v^*)^2) - \frac{b}{\tau} = 0. \tag{3.34}$$

Moreover, as we want them to be imaginary, the discriminant of the formula to obtain the values of $\lambda_{1,2}$, must be negative:

$$\Delta = Tr(A)^2 - 4Det(A) < 0 \Rightarrow Tr(A)^2 < 4Det(A) \Rightarrow Det(A) > \frac{1}{4}Tr(A)^2 = 0.$$

5. Finally, what we are really interested in is to find the I values in which we have a Hopf bifurcation, so using the previous points, we obtain:

$$\begin{cases} (v^*)^3 - \dfrac{3(b-1)}{b}v^* + \dfrac{3a}{b} - 3I = 0 \\ Tr(A) = 1 - (v^*)^2 - \dfrac{b}{\tau} = 0, \end{cases}$$

$$\Rightarrow \left(\pm\sqrt{1 - \frac{b}{\tau}}\right)^3 - \frac{3(b-1)}{b}\left(\pm\sqrt{1 - \frac{b}{\tau}}\right) + \frac{3a}{b} - 3I = 0$$

$$\Rightarrow I = \frac{1}{3}\left(\pm\sqrt{1 - \frac{b}{\tau}}\right)^3 - \frac{b-1}{b}\left(\pm\sqrt{1 - \frac{b}{\tau}}\right) + \frac{a}{b} \tag{3.35}$$

Once we have seen how to find the values of I to arrive to the Hopf Bifurcation, let us use the values of the FitzHugh-Nagumo model $a = 0.7$, $b = 0.8$ and $1/\tau = 0.08$ in the equation (3.35). Hence, we see that the two values of I where we have the Hopf bifurcation are:

$$\Rightarrow I_+ = \frac{1}{3}(\sqrt{1 - 0.8 \times 0.08})^3 - \frac{0.8 - 1}{0.8}\sqrt{1 - 0.8 \times 0.08} + \frac{0.7}{0.8} \approx 1.41 \tag{3.36}$$

$$\Rightarrow I_- = \frac{1}{3}(-\sqrt{1 - 0.8 \times 0.08})^3 + \frac{0.8 - 1}{0.8}\sqrt{1 - 0.8 \times 0.08} + \frac{0.7}{0.8} \approx 0.331 \tag{3.37}$$

Since here we have only found that there is a periodic cycle, however it stil remainds to study its stability. To get that, first we are going to calculate the values of $\lambda_{1,2} = \gamma_{1,2}(I_\pm)i = \pm\frac{\sqrt{4Det(A)}}{2}$ because in I_+ and I_- the Tr(A) = 0. So, using the values of our model, we obtain $\lambda_{1,2} = \pm 0.276i$. Now it is needed to calculate the values of what in the theorem was called F and G to determine the direction and stability of the Hopf bifurcation. So we are going to follow the next steps.

- It is time to calculate the value of what is called c_1 in the *theorem*. Taking $F = v - \frac{v^3}{3} - w + I$ and $G = \frac{1}{\tau}(v + a - bw)$, we obtain the resulting values (depending if we evaluate in λ_1 or λ_2:

$$c_1 = \frac{1}{16 \times (\pm 0.276)}(0) + ((-2) + 0 + 0 + 0) = -2 \Rightarrow c_1 < 0 \tag{3.38}$$

- Finally it remains to calculate the sign of what is called $\dfrac{\partial\alpha(a)}{\partial a}(a_c)$ in the *theorem*.

$$\alpha(a) = Tr(A) = 1 - (v^*(I))^2 - \frac{b}{\tau} \Rightarrow \frac{\partial\alpha(a)}{\partial a} = -2v^*(I) \tag{3.39}$$

  In our specific case, we have:

$$v^* = \pm\sqrt{1 - \frac{b}{\tau}} = \pm 0.967 \Rightarrow \frac{\partial\alpha(a)}{\partial a}(a_c) = -2v^*(I_\pm) = -2(\pm 0.967) = \mp 1.93. \tag{3.40}$$

Taking the values of the equations from (3.36) to (3.40), we can say that there are two Hopf bifurcations:

1. $\lambda_1 = +0.276i$ I is created for the value of $I = I_+ \approx 1.41$. It has $c_1 = -2 < 0$ and $\frac{\partial\alpha(a)}{\partial a}(a_c) = -1.93$. Sothat, for $I < 1.41$ there are stable periodic orbits.

2. $\lambda_1 = -0.276i$ I is created for the value of $I = I_- \approx 0.331$. It has $c_1 = -2 < 0$ and $\frac{\partial \alpha(a)}{\partial a}(a_c) = 1.93$. So that, fo $I > 0.33$ there are stable periodic orbits.

In conclusion, we have two unstable Hopf bifurcations when $I = I_-$ and $I = I_+$, moreover between these two Hopf bifurcation, there is located an stable periodic orbit. It can be appreciated in the Figure 3.5.

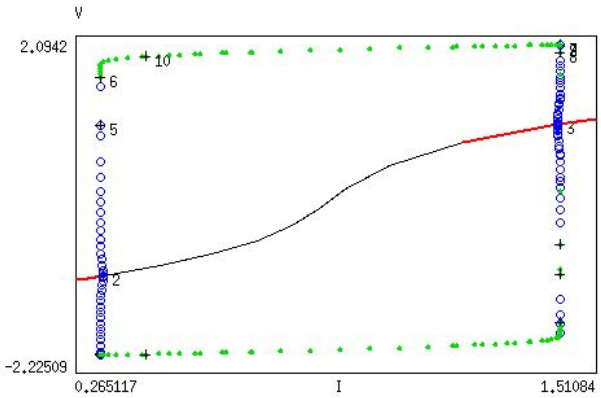

Figure 3.5: Two unstable Hopf bifurcations in $I_- = 0.331$ and $I_+ = 1.41$. The blue and green path describes the stable periodic orbit between I_- and I_+.

4

Modelization of networks

IN this chapter we want to study the behavior of different networks of neurons by its synchronization. To make things easier and get simple models, we are going to divide in two all the possible systems: fast and slow. It has been seen that complex population firing patterns have an important role in some brain functions: oscillatory behavior, sensory processing, ... To locate the activity and see if it propagates and how or if it remains in a located place is a very complicated point. There are few things to keep in mind when synchronizing neurons and making a network:

1. Specific properties of cells behave independently. The first things to determine are the channel gating variables.

2. Synaptic properties of connections between neurons. There exist different classes: electrical or chemical (excitatory or inhibitory).

3. Kind of network connectivity. It can be sparse (each neuron communicate with a small number of neurons), dense (there are a lot of connections between neurons). Moreover, the connectivity between neurons can be structured or not.

Our purpose is to consider two-variable neuron models and classify the type of activity patterns we obtain to understand how they depend on the cells, synapses and network

structure. We are going to modelize independently each of the three important concepts when talking about a neuronal network. Finally, we get a unified model to study its behavior.

4.1 Synaptic connections

In this section the objective is to find a model which expresses how a network with two mutually coupled neurons works. However, the first important thing is to define some new (and remember other that we have already seen) variables and parameters:

- I_{syn}: synaptic current.
- $\hat{g}_{syn}$: maximal conductance.
- s: fraction of open channels which depends on the presynaptic membrane potential and satisfies:
$$\frac{ds}{dt} = \alpha(1-s)H_\infty(v_{pre} - v_T) - \beta s, \tag{4.1}$$
where H_∞ is the smooth approximation of the Heaviside step function, v_T the threshold at which, when the applied current is below it, the membrane potential returns quickly to the rest, and if the current is above it, there is an action potential, and α, β the rates at which the synapse turns on/off respectively.
- v_{post}: membrane potential of the postsynaptic cell.
- v_{syn}: the synaptic reversal potential, which $v_{syn,EXC} \simeq 0\ mV$ if it is an excitatory cell and $v_{syn,INH} \simeq -80\ mV$ if it is an inhibitory cell.

With all these variables, we get the formula: $I_{syn} = \hat{g}_{syn}s(v_{post} - v_{syn})$. From here, if we get two neurons and join them, assuming that $i \neq j$ and that the neurons are identical (so f and g does not depend on the neuron), we obtain the system:

$$\begin{cases} \dfrac{dv_i}{dt} = f(v_i, w_i) - \hat{g}_{syn}s_j(v_i - v_{syn}) \\ \dfrac{dw_i}{dt} = \epsilon g(v_i, w_i) \\ \dfrac{ds_i}{dt} = \alpha(1-s_i)H_\infty(v_i - v_T) - \beta s_i. \end{cases} \tag{4.2}$$

We have supposed that the coupling between the two neurons is through the synaptic variables where the first is the presynaptic and the second the postsynaptic. What

this system (4.2) really means is that when the first neuron fires a spike, v_1 crosses v_T and s_1 activates at a rate which depends on α and β, making changes on the v_2. Otherwise, when the first neuron is silent, which means that ($v_1 < v_T$), s_1 decays at rate β.

To classify the different kinds of synapses, it is as easy as changing some variables. Classifying depending on excitatory or inhibitory synapses is just needed to change the value of v_{syn}. Classifying depending on the rate at which they activate or deactivate depends on the parameters α and β. The last classification to consider is if the synapses is direct or indirect, but as we have considered that the neuron activates when its potential crosses the v_T, our system is based on direct synapses. However, it is possible to modelize an indirect synapsis, although it is a bit more complicated. It is needed to define new independent neurons x_i and change the last equation of the system (4.2) by:

$$\begin{cases} \dfrac{dx_i}{dt} = \epsilon\alpha_x(1-x_i)H_\infty(v_i - V_T) - \epsilon\beta_x x_i \\ \dfrac{ds_i}{dt} = \alpha(1-s_i)H_\infty(x_i - \omega_x) - \beta s_i. \end{cases} \tag{4.3}$$

In this case, the variables $\alpha, \beta, \alpha_x, \beta_x$ are independents from ϵ. x is the variable that expreses a secondary process which is activated when transmitters connect to the postsynaptic cell. The effect of this kind of synapses is to consider the time between the first neuron starts the process until the second neuron feels it.

4.2 Example of synchronization

Let us suppose we have two neurons and each of them has an oscillatory behavior without any coupling with a specific I, and let us call C_0 the nullcline described. We want to see what happens if we apply a fast, direct synapsis between these two neurons. Remember that we have seen that there are the silent and active phases, and from one phase to another the cells have to jump up and down when they reach the left or right knee of the cubic. We are going to suppose that they begin in the silent phase and that they are close enough to each other. Let us see the four stages they come across during a cycle, until the first neuron is in the initial point again. The period can be seen schematized in the Figure 4.1.

1. The *neuron 1* is the first to jump down. It raises the cubic corresponding to *neuron 2*, creating the cubic C_A. The fast equation, forces *neuron 2* to jump up to the active phase.

2. Both neurons are in the active phase along the right branch of C_A, but this time the *neuron 2* is ahead, while in active phase was *neuron 1*.

3. *Neuron 2* reaches the right knee of C_A, so it is the first to jump down decreasing the cubic of *neuron 1* from C_A to C_0. As *neuron 1* is above the right knee of C_0, it will jump down.

4. Both neurons lie on the left branch of C_0 and with the same order as they were at the beginning, with *neuron 1* under the other. So when it reaches the point from where it began, it's said that a full cycle is completed.

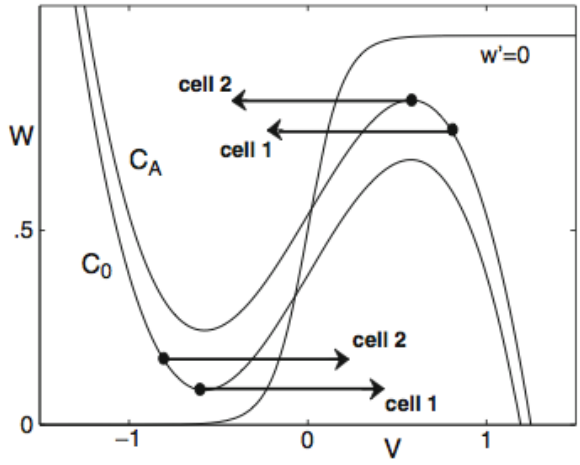

Figure 4.1: Example of two coupled neurons *neuron 1* and *neuron 2*, which initially lie in the C_0 cubic. The C_A cubic appears when the *neuron 1* jumps up and there is created the synaptic current. From [4].

4.3 Network structures

Although there exist multiple structures to determine, we are going to modelize the network in a way in which the structure is defined with the following system:

$$\begin{cases} \dfrac{dv_i}{dt} = f_i(v_i, w_i) - g^i_{syn}\left(\sum_i W_{ij}s_j\right)(v_i - v^i_{syn}) \\ \dfrac{dw_i}{dt} = \epsilon g_i(v_i, w_i) \\ \dfrac{ds_i}{dt} = \alpha_i(1 - s_i)H_\infty(v_i - v_T) - \beta_i s_i. \end{cases} \tag{4.4}$$

This system is considered to have excitatory neurons and inhibitory neurons. The variables $v_{syn}, \alpha_i, \beta_i$ depend on the neuron i and the sum is made over all presynaptic

neurons, where W_{ij} expresses the probability of having a connection between the neurons i and j.

However, it is necessary to limit the number of neurons which interact. So let us determine the domain D which delimits the neurons on the network, and let $v(x,t)$ be the membrane potential of a cell at the position $x \in D$ and time t. Considering homogeneous neurons, we obtain the system:

$$\begin{cases} \dfrac{\partial \nu}{\partial t} = f(v(x,t), w(x,t)) - g_{syn}(v(x,t) - v_{syn}) \int\limits_{y \in D} W(x,y)s(y,t)dy \\ \dfrac{\partial w}{\partial t} = \epsilon g(v(x,t), w(x,t)) \\ \dfrac{\partial s}{\partial t} = \alpha(1 - s(x,t))H_\infty(v(x,t) - v_T) - \beta s(x,t). \end{cases} \tag{4.5}$$

It is a way to express the networks of neurons in a continuous model.

5

Synchronization in a FitzHugh-Nagumo network

Taking advantage of the Rubin-Terman model and using what we have been studying in the previous chapters, it is the moment to see the behavior of the neurons with the FitzHugh-Nagumo model. Through this section we are going to show how it is done the coupling between neurons which are modeled with FitzHugh-Nagumo equations. Moreover, with analytical calculations and simulating the system numericaly in *python*, we are going to study how vary the synchronization of the system depending on the coupling strenght between neurons.

5.1 Single neuron model

Let us take again the system defined in (3.29), which determines the behavior of single neuron.

$$\begin{cases} v' = v - \dfrac{v^3}{3} - w + I \\ w' = 0.08(v + 0.7 - 0.8w). \end{cases} \tag{5.1}$$

The w-nullcline can be approximated as a line and the v-nullcline as a cubic depending on the I value. This value, is going to determine the equilibrium points of the system

and with that, we are going to see if we obtain a periodic orbit or a fixed point. We have seen that, when the v-nullcline and w-nullcline have the equilibrium point in the middle part of the cubic, such as happens with $I = 1$, we obtain a periodic solution, while if the intersection is in the left or right hand, the solution stops in the equilibrium point. To change the equilibrium point, is as easy as vary the value of I. In the Figure 5.1, we can see that when the neuron begins on their initial point, it immediately goes to the nearest nullcline, and from there, it starts to define its periodic orbit.

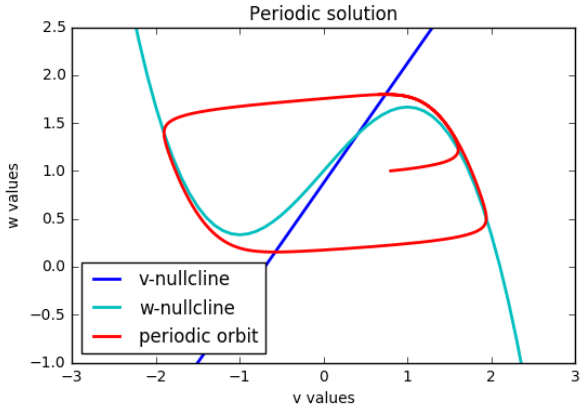

Figure 5.1: The periodic orbit seen in the phase plane with $I = 1$ and initial values $(v_0, w_0) = (0.8, 1)$.

This periodic orbit described by a neuron with $I = 1$, is actually a group of spikes of potential v. In the following Figure 5.2, it is possible to see the different spikes that, each spike respresents a periodic orbit.

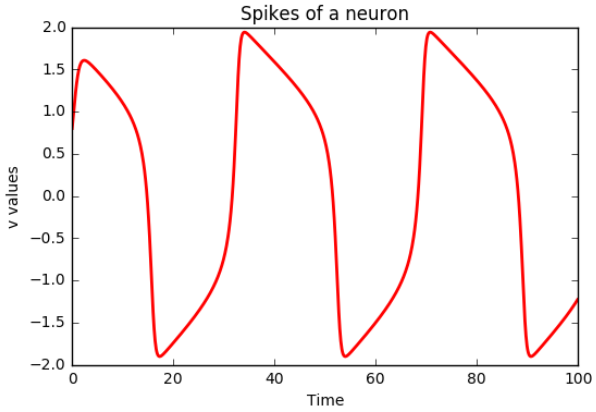

Figure 5.2: The spikes of a neuron with $I = 1$ which describes periodic orbits.

5.2 Network activity

To proceed with this section, it is important to define the coupling between neurons in a network. The coupling is called synaptic coupling and in our network, it is going to be described like:

$$I_{syn} = g_{syn}\left(\sum_{k=1}^{N} s_\infty(v_k)\right)(v_{syn} - v_j) \text{ where } s_\infty(v) = \frac{1}{1 - e^{\frac{v-v_h}{v_s}}} \approx H(v - v_h), \tag{5.2}$$

being $H(v - v_h)$ the Heaviside step function, and v_h, v_s some constants. This synaptic coupling is what is going to define different kinds o synchronizations, and following the J. Rubin and D. Terman study in [3] we are going to try to find some analytic conditions for the FitzHugh-Nagumo model in the following section 5.3.

We are going to consider a population of N neurons and assume that we have an homogeneous coupling, which means that all coupling will behave equally and with no distinction between cells. The value of $g_{syn} > 0$ represents the maximal synaptic conductance and v_{syn} the synaptic reversal potential. In the model, each neuron propertie is going to be defined as (v_i, w_i), with $i = 1, \ldots, N$.

So, using the system (4.4), applying our assumptions, we obtain the resulting network of N coupled neurons that, for each neuron $j = 0, ..., N$:

$$\begin{cases} v_j' = v_j - \dfrac{v_j^3}{3} - w_j + I_j + g_{syn}\left(\sum\limits_{i=0}^{N} s_\infty(v_i)\right)(v_{syn} - v_j) \\ w_j' = 0.08(v_j + 0.7 - 0.8w_j) \\ I' = 0. \end{cases} \tag{5.3}$$

5.3 One:one synchronization

As said previously, the main goal of this section is to study analytically some conditions in which we have 1:1 synchrony, it means, when all the neurons oscillate with the same period very close to each other, in the FitzHugh-Nagumo model as J. Rubin and D. Terman did in the study of their model in [3].

5.3.1 Analysis of snakes

First of all, let us define what is a snake of synchrony in this context. A *snake of synchrony* is a curve described by the evolution of the positions of all of the cells at each fixed time.

All cells become active on each cycle of network and jump up and down together. What is done in the precedent analysis is the parametrization of the snake by the parameter I_{app}.

We are going to derive an analytic expression for a periodic solution of:

$$\begin{cases} v' = v - \dfrac{v^3}{3} - w + I_{app} + I_{syn} \\ w' = 0.08(v + 0.7 - 0.8w) \\ I' = 0, \end{cases} \tag{5.4}$$

where $I_{syn} = g_{syn}\left(\sum_{k=1}^{N} s_\infty(v_k)\right)(v_{syn} - v_j)$ as we have described in the equation (5.2). Our aim is to obtain a snake of synchrony in which all the cells become active on each cycle of network activity. The first thing we are going to assume is that all cells jump up and down together, which means that a large enough g_{syn} is needed. In this case, the snake will be parametrized by the parameter I_{app} that will be called I in this chapter to simplify notation. From now on, the snake will be denoted by $(v(I,t), w(I,t))$ for $I_{min} = 0.1 \leq I \leq I_{max} = 0.35$ in our modelization.
To proceed with the analysis, we are going to make some assumptions:

- The snake starts in the silent phase with the neuron (or neurons) with maximum applied current $I_{max} = 0.35$ at the left knee, ready to jump.

- The neurons are uniformly distributed with the v values from -2 to -1.5, and the w values from 1 to 0.

- The analytic formula is obtained when the snake returns after one complete cycle to the exact position from which it started. We are going to follow it in the phase space until the cycle is completed.

To analyze the behavior of the snake it is usual to analyze the evolution over each of the four phases of the cycle: the jump-up, the active phase, the jump-down and the silent phase. We derive the formula of the snake's position at jump-up, however it could be calculated similarly from other stages of the cycle.

The silent and active phases

First of all, let us introduce the slow time scale seen in the subsection 3.2.2: $\tau = \epsilon t$ in the system and define $I_{tot}(I,t) = I + I_{syn}(I,t)$ to obtain the system with respect to τ:

$$\begin{cases} v' = v - \dfrac{v^3}{3} - w + I_{tot} \\ w' = 0.08(v + 0.7 - 0.8w). \end{cases} \tag{5.5}$$

We are going to refer to the branches of the first nullcline of the cubic as: $v = v_L(w, I_{tot})$ and $v = v_R(w, I_{tot})$. Substituting into the second equation we obtain that the solutions for the w satisfy the equation: $w' = g(v_\alpha(w, I_{tot}), w) \equiv G_\alpha(w, I_{tot}) \approx -\rho w + c_\alpha + b_\alpha I_{tot}$ where $\alpha = L$ or R depending on whether the cell lies in the silent or active phase respectively.

This is an important point of the thesis. How are we going to obtain the linear approximations of the $w' = G_\alpha(w, I_{tot})$? On one hand, for the right branches, we are going to take the v in the interval $[1, 4]$, on the other hand, for the left branches, we are going to take the v in the interval $[-4, -1]$. With numerical approximation we are going to calculate the linear regresion in the small intervals from $[1, 4]$ and $[-4, -1]$. Finally, we are going to get a general expression depending on the variable I.

Using this method, we have obtained the following values of the varialbes: $\rho \approx -0.957$, $c_R \approx 2.48$, $c_L \approx -1.08$ and $b_L = b_R \approx 0.157$. During the study we are not going to use the values, to make the notation easier. Assuming that $I_{syn} = 0$ (this will only happen when the neuron is located in the silent phase), we get the general solution:

$$w_\alpha(t) = w_0 e^{-\rho t} + \Lambda_I^\alpha (1 - e^{-\rho t}) \text{ with } \Lambda_I^\alpha = \frac{c_\alpha + b_\alpha I}{\rho}. \tag{5.6}$$

- **Active phase:** The cells lie along the right branches of the cubic. As we have seen, the linear approximation of the right branch of the cubicis the resulting equation:

$$w' \approx -\rho w + c_R + b_R I_{tot}. \tag{5.7}$$

- **Silent phase:** The cells lie along the left branches of the cubic. Following the process, we find a linearization of w' which is:

$$w'_L \approx -\rho w + c_L + b_L I_{tot}. \tag{5.8}$$

- We are going to use the notation $w_{LK} = w_{LK}(I_{max})$ for the w-value of the left knee of the v-nullcline for $I = I_{max}$. Since we assume that there are no fixed points on the

left branch of the v-nullcline for the I_{max}, we have: $w'_L \approx -\rho w_{LK} - c_L + b_L I_{max} < 0$. Let us verify it happens in our model:

$$w_{LK} = w_{LK}(I_{max}) = w_{LK}(0.35) = -1 - \frac{(-1)^3}{3} + 0.35 = -0.317$$

$$\Rightarrow w'_L \approx -0.957(-0.317) - 1.08 + 0.157(0.35) = -0.722 < 0$$

Jumping up and jumping down

The aim is to derive an expression for when all the cells jump up together. It is important to see that the simultaneous jump up is possible thanks to the fact that when a cell jumps up, there is an increase of synaptic input of the other cells, letting them to jump up at that moment. Another relevant fact is that the jump-up takes place on fast time scale, which causes that all cells jump up together respect to the slow time scale. The procedure to obtain the derivation is following the next steps:

1. Assume that all cells with $I_{app} = I_{max} = 0.35$ jump up together when they reach the left knee.

2. If we fix an applied current $I \in [0.1, 0.35]$, each of the cells with $I < I_{app} < 0.35$ will jump up at the same moment as cells with I_{max}.

The big question is: will the cell with $I_{app} = I$ (denoted $cell(I)$) jump up at the same moment? Let's see it.
We have previously defined the synaptic input of a neuron as:

$$I_{syn} = g_{syn} \left(\sum_{k=1}^{N} s_\infty(v) \right) (v_{syn} - v). \tag{5.9}$$

A moment before the input, the $cell(I)$ has the value of $w = w(I)$ and it will experiment a jump-up if $w < w_{LK}$ (w is under the left knee) by increasing the value of $w_{LK}(I)$ to $w_{LK}(I + I_{syn}(I))$. Then, the $cell(I)$ will jump up if it verifies $w(I) < w_{LK}(I + I_{syn}(I))$. Hence, if it is satisfied for all $I \in [I_{min}, I_{max}]$, then all cells will jump up together.
Concerning the jump-down, we are going to consider that all the cells jump down at the same time respect to τ, from the right knee $w_{RK}(I)$. This is possible through a mechanism analogous to that described above for synchronous jump-up. The jump-down starts at the time that $cell(I_d)$ reaches the right knee for some applied current $I_d \in [I_{min}, I_{max}]$ rising the right knee of other cells. Hence, if $w(I) > w_{RK}(I + I_{syn}(I))\ \forall I$ all cells will jump down together.

5.3.2 Linear Snakes

Snake formula

Throughout this section we are going to assume that all cells jump up and down together (respect to the slow time scale). The aim is to derive an explicit formula for the initial position (in the silent phase) $w(I) = w(I, 0)$ of a periodic snake of synchrony.

- **Jump-down**: We assume that $cell(I_d)$ is going to be the first cell to jump down from the right knee and that w^d_{RK} is the notation of its position. We have to notice that, as we are in the active phase, $I_{syn} \neq 0$, so $I_{tot} = I_d + I^{TOT}_{syn}$. As it is quite difficult to calculate that I^{TOT}_{syn}, we are going to define it with all the values of s equal to 1, so we obtain $I^{TOT}_{syn} = g_{syn}(v_{syn} - v(I_{tot}))$. Moreover, it is important to notice that the time that a cell spends in the active phase after it jumps up is equivalent to the time for $cell(I_d)$ to evolve from $w_d \equiv w(I_d)$ to the w^d_{RK} under the equation $w' \approx -\rho w + c_R + b_R I$. Hence, to find that time T_A, we are going to use the general solution (5.6):

$$w^d_{RK} = w_d e^{-\rho T_A} + \tilde{\Lambda}^\alpha_D(1 - e^{-\rho T_A}) = \tilde{\Lambda}^\alpha_D + (w_d - \tilde{\Lambda}^\alpha_D) \text{ where } \tilde{\Lambda}^\alpha_D = \frac{c_R + b_R(I_d + I^{TOT}_{syn})}{\rho}. \tag{5.10}$$

$$\Rightarrow e^{-\rho T_A} = \frac{w^d_{RK} - \tilde{\Lambda}^\alpha_D}{w_d - \tilde{\Lambda}^\alpha_D} \Rightarrow T_A = \frac{1}{\rho} \ln\left(\frac{w_d - \tilde{\Lambda}^\alpha_D}{w^d_{RK} - \tilde{\Lambda}^\alpha_D}\right). \tag{5.11}$$

  So that, the resulting T_A is the time that the $cell(I_d)$ spends in the active phase.

  Using the (5.10) and (5.11) equations, it is possible to define the position of $cell(I)$ after a time T_A in the active phase:

$$w(I, T_A) = \tilde{\Lambda}^\alpha_I + (w(I) - \tilde{\Lambda}^\alpha_I)\frac{w^d_{RK} - \tilde{\Lambda}^\alpha_I}{w_d - \tilde{\Lambda}^\alpha_I} = \tilde{\Lambda}^\alpha_I \left(\frac{w_d - w^d_{RK}}{w_d - \tilde{\Lambda}^\alpha_I}\right) + w(I) \left(\frac{w^d_{RK} - \tilde{\Lambda}^\alpha_I}{w_d - \tilde{\Lambda}^\alpha_I}\right). \tag{5.12}$$

- **Silent phase**: It happens after the jump-down, and now it is valid that $I_{syn} = 0$. In this stage, all the cells evolve according to the equation $w'_L \approx -\rho w + c_L + b_L I$. In this phase, the initial position is $w(I, T_A)$. Using again the general expression (5.6) we obtain the position of a neuron, when located in the silent phase at time τ:

$$w(I, \tau) = \left[\tilde{\Lambda}^\alpha_I \left(\frac{w_d - w^d_{RK}}{s_d - \tilde{\Lambda}^\alpha_I}\right) + w(I) \left(\frac{w^d_{RK} - \tilde{\Lambda}^\alpha_I}{w_d - \tilde{\Lambda}^\alpha_I}\right)\right] e^{\rho(T_A - \tau)} + \Lambda^L_I(1 - e^{\rho(T_A - \tau)}). \tag{5.13}$$

Valuated in $I = I_{max}$ and definit $T_S = T - T_A$ the time a neuron spends in the silent phase, we obtain:

$$w_{LK} = \left[\tilde{\Lambda}_M^\alpha \left(\frac{w_d - w_{RK}^d}{s_d - \tilde{\Lambda}_I^\alpha}\right) + w_{LK}\left(\frac{w_{RK}^d - \tilde{\Lambda}_I^\alpha}{w_d - \tilde{\Lambda}_I^\alpha}\right)\right] e^{-\rho T_S} + \Lambda_M^L(1 - e^{-\rho T_S}). \quad (5.14)$$

Multiplying by $\dfrac{w(I)}{w_{LK}}$, it remains:

$$w(I) = \left[\frac{w(I)}{w_{LK}}\tilde{\Lambda}_M^\alpha \left(\frac{w_d - w_{RK}^d}{s_d - \tilde{\Lambda}_I^\alpha}\right) + w(I)\left(\frac{w_{RK}^d - \tilde{\Lambda}_I^\alpha}{w_d - \tilde{\Lambda}_I^\alpha}\right)\right] e^{-\rho T_S} + \frac{w(I)}{w_{LK}}\Lambda_M^L(1 - e^{-\rho T_S}). \quad (5.15)$$

- Equating the (5.13) and the (5.15) equation, we obtain:

$$\left(\tilde{\Lambda}_I^\alpha - \frac{w(I)}{w_{LK}}\tilde{\Lambda}_I^\alpha\right)\left(\frac{w_d - w_{RK}^d}{w_d - \tilde{\Lambda}_D^\alpha}\right) e^{-\rho T_S} + \left(\Lambda_I^L - \frac{w(I)}{w_{LK}}\Lambda_M^L\right)(1 - e^{-\rho T_S}) = 0. \quad (5.16)$$

Jump up condition

At this point we want to find conditions to assure the synchrony. Using $w(I) < w_{LK}(I + I_{syn}(I))$, we follow the next steps:

1. Let us choose λ_1 so that if (v, w) is in the silent phase (with $I_{syn} = 0$), then $v_{syn} - v > \lambda_1$. As we have $v_{syn} = 0.8$ and in the silent phase, $v \in [-4, -1]$ so $v_{syn} - v \in [1.8, 4.8]$. With what we have seen, we are going to take, for example, the value of $\lambda_1 = 1$ because it verify the inequality $v_{syn} - v > \lambda_1$.

2. Let us assume that there exists $\lambda_2 > 0$ so that $\sum_{k=1}^{N} s_\infty(v_k) \geq \lambda_2(I_{max} - I) \quad \forall I \in [I_{min}, I_{max}]$. So let us take, for example, $\lambda_2 = 40$. I have chosen this value because $\sum_{k=1}^{N} s_\infty(v_k) \leq 20$ and $(I_{max} - I) \in [0, 0.25]$. Hence, the maximum value that λ_2 can be is $\sum_{k=1}^{N} s_\infty(v_k)/(I_{max} - I) = 4$. So that, let us take, for example $\lambda_2 = 2$.

3. Let us set $\lambda_0 = \lambda_1\lambda_2 = 1 \times 2 = 2$ and substituting in the definition of the synaptic input to a cell we obtain:

$$I_{syn} \equiv g_{syn}\left(\sum_{k=1}^{N} s_\infty(v_k)\right)(v_{syn} - v) \geq g_{syn}(v_{syn} - v)\lambda_2(I_{max} - I) >$$

$$> g_{syn}(I_{max} - I)\lambda_1\lambda_2 = g_{syn}(I_{max} - I)\lambda_0 = 0.02(0.35 - I)2 = 0.014 - 0.04I.$$

4. Let us assume that it is possible to bound $w_{LK}(I)$ between two linear functions of I in the following way:

$$\exists m_1, m_2 : \ m_1(I_{max} - I) < w_{LK}(I) - w_{LK} < m_2(I_{max} - I) \ \ \forall I \in [I_{min}, I_{max}].$$

As we know that $w_{LK}(I) = -1 - \frac{(-1)^3}{3} + I \in [-0.567, -0.317]$ it is possible to asure that $-0.25 \leq w_{LK}(I) - w_{LK} \leq 0$, we can define $m_1 = -2$ and $m_2 = 2$.
Mixing this with previous assumptions and conditions, we arrive to:

$$w_{LK}(I + I_{syn}) < w_{LK} + m_2(I_{max} - I)(1 - g_{syn}\lambda_0) = -0.317 + 2(0.35 - I)(1 - 0.02 \times 2)$$

$$\implies w_{LK}(I + I_{syn}) < 0.355 - 1.92I.$$

5. To get more conditions, we observe that:

$$\left.\begin{aligned} w(I) &< w_{LK}(I + I_{syn}(I)) \\ w_{LK}(I + I_{syn}) &< w_{LK} + m_2(I_{max} - I)(1 - g_{syn}\lambda_0) \end{aligned}\right\} \tag{5.17}$$

$$\Rightarrow g_{syn} < \frac{1}{\lambda_0}\left(1 - \frac{w(I) - w_{LK}}{m_2(I_{max} - I)}\right). \tag{5.18}$$

The value of $w(I)$ from the inequality (5.18) can be replaced by the equation (5.15). Due to the complexity of the equation, the following calculations are complicate, because they depend on the value of T and I_d. This means that the configuration of the network depends on the period and the value of I_d of the $cell(I_d)$.

5.4 Specific example

In the last section we have calculated a very acurate G_R, arriving to a complex condition (5.16) to work with. However, in the Rubin-Terman study, they get $w' \approx -\rho w$ in the active phase, with an easier expression equivalent to our (5.16). So, in this section we are going to rewrite all the process in the previous section, with the specific valules of the variables $b_R = c_R = 0$ to adjust our equations independently from I.

- The right branches of the cubics are going to be linearized with the equation $w' \approx -\rho w$. While the silent phase is going to remain equaly defined as before. That causes a change of all the formulas related to the active phase.

- The time T_A is going to be different. To calculate it we are going to follow the same process as the section 5.3.2:

$$w_{RK}^d = w_d e^{-\rho T_A} \Rightarrow e^{-\rho T_A} = \frac{w_{RK}^d}{w_d} \Rightarrow T_A = \frac{1}{\rho} \ln\left(\frac{w_d}{w_{RK}^d}\right), \tag{5.19}$$

$$w(I, T_A) = w(I)\frac{w_{RK}^d}{w_d}. \tag{5.20}$$

- Once calculated the behavior on the active phase, it is the time to express the silent phase equations for this example:

$$w(I, \tau) = w(I)\frac{w_{RK}^d}{w_d} e^{\rho(T_A - \tau)} + \Lambda_I^L(1 - e^{\rho(T_A - \tau)}), \tag{5.21}$$

$$w_{LK} = w_{LK}\frac{w_{RK}^d}{w_d} e^{-\rho T_S} + \Lambda_M^L(1 - e^{-\rho T_S}). \tag{5.22}$$

As we have already done in the previous section, we multiply the equation (5.22) by $\dfrac{w(I)}{wLK}$ and obtain:

$$w(I) = w(I)\frac{w_{RK}^d}{w_d} e^{-\rho T_S} + \frac{w(I)}{w_{LK}}\Lambda_M^L(1 - e^{-\rho T_S}). \tag{5.23}$$

Substituing the equations (5.21) in the (5.23), we get:

$$\left(\Lambda_I^L - \frac{w(I)}{w_{LK}}\Lambda_M^L\right)(1 - e^{-\rho T_S}) = 0 \Rightarrow w(I) = w_{LK}\frac{\Lambda_I^L}{\Lambda_M^L}. \tag{5.24}$$

- Taking the system (5.17) in our example, we obtain:

$$\begin{cases} w(I) < w_{LK}(I + I_{syn}) \\ w(I) = w_{LK}\dfrac{\Lambda_I^L}{\Lambda_M^L} \\ w_{LK}(I + I_{syn}) < w_{LK} + m_2(I_{max} - I)(1 - g_{syn}\lambda_0) \end{cases} \tag{5.25}$$

$$\Rightarrow g_{syn} < \frac{1}{\lambda_0}\left(1 - \frac{w_{LK}\frac{\Lambda_I^L}{\Lambda_M^L} - w_{LK}}{m_2(I_{max} - I)}\right). \tag{5.26}$$

Taking the previously calculated values $w_{LK} = -0.317$, $\Lambda_M^L = 1.07$ and $\Lambda_{I_{min}}^L = 1.11$, we obtain that the minimum value of the right part of the inequality is 0.512. Hence, for the value of $g_{syn} = 0.02$ it is verified, so we have a periodic snake.

5.5 Simulations

To verify the results obtained in the preceding sections, we have done a script in python, see the Appendix. We have also studied numerically how is the synchrony depending on the g_{syn} values. The integration is calculated by *odeint* command in python, so it is integrated with the Runge-Kutta method. It is quite a good method because has fourth order and relative and absolute tolerances of 10^{-8}.

First of all let us define some initial condiitons:

- We are taking a network of $N = 20$ neurons. The neurons are colored in the graphics depending on the value of the I_{app} they have.
- $I_{min} = 0.1$ and $I_{max} = 0.35$. For the other neurons, we are going to divide the interval $[0.1, 0.35]$ by 20, and each neuron is going to take one of the different values.
- The initial values for v are uniformly divided of the interval $[-2, -1.5]$. The same has been done for the w initial values but taking the interval $[0, 1]$.
- $v_{syn} = 0.8$.
- g_{syn} is the parameter we are going to change to see the different behaviors of the network. Thus, we are going to investigate how the coupling strenght between pair of cells affects the dynamics of the network.

To proceeding with the different cases of the network depending on the g_{syn} values, it is interesting to see that, depending on the values of the I, the neurons have different resulting cubics. So, if we take values from $I = -1.5$ to $I = 1.5$ we are going to obtain the following nullclines shown in Figure 5.3.

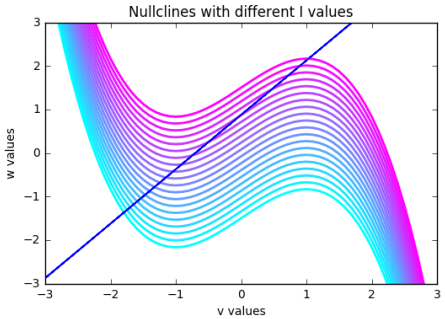

Figure 5.3: Nullclines of the FitzHugh-Nagumo model, where there have been chosen different values for the I. They are from $-1,5$ to 1.5.

Now, it is the moment to see the different behaviors of the networks, depending on the g_{syn}. I have only exposed three examples and with specific values. Those, correspond to what I have found previously, that for g_{syn} minor than some values, it looses the regularity.

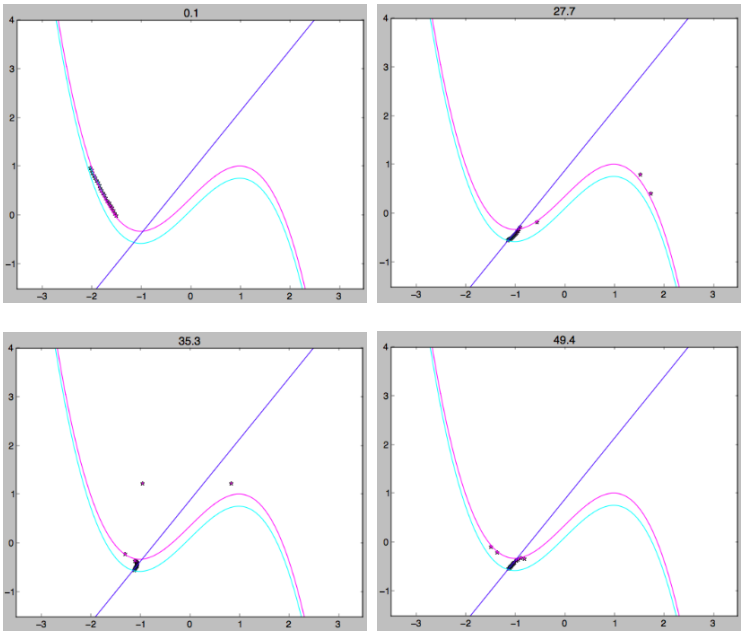

Figure 5.4: With $g_{syn} = 0$, only two neurons have enough input current to jump up to the active phase. The rest of the neurons do not have enough impulse, so they remain on the middle branch of the cubic until the first two neurons finish their cycle and come back to the silent phase.

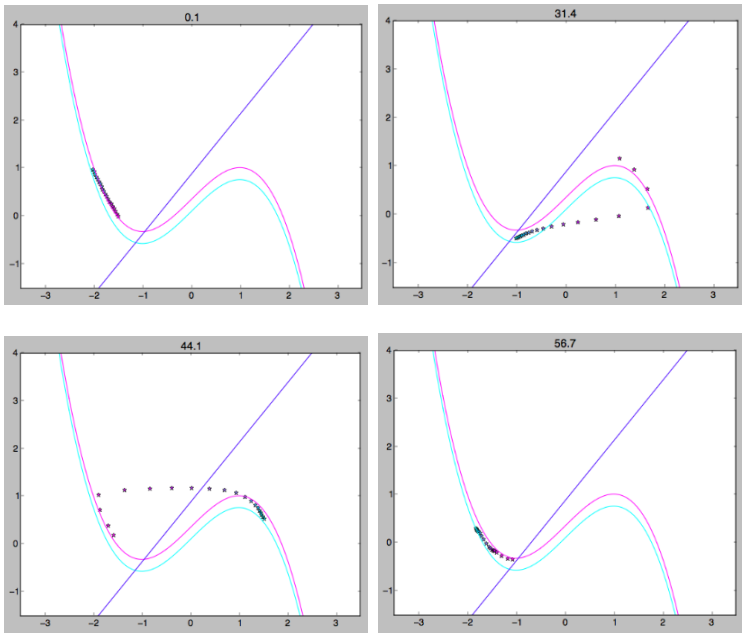

Figure 5.5: For $g_{syn} = 0.02$, we obtain a network that behaves in a regular way. All the neurons respect their order in the network and describe periodic orbits.

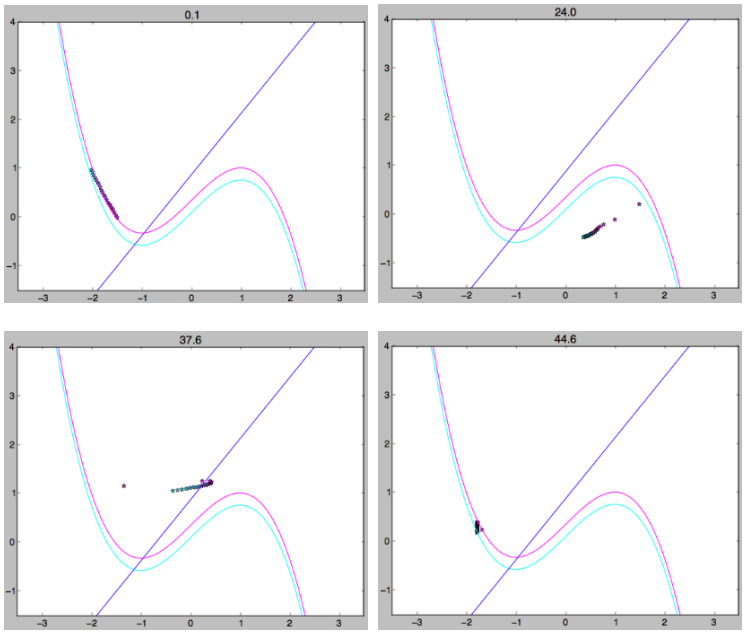

Figure 5.6: When $g_{syn} = 2.0$, the neurons on the network changes their order when they finish the cycle.

6
Conclusions

This thesis has been one of my bigest challenges during the degree. I never realised how some courses I took during my studies would be this useful when applying mathematics to the real world, and even to model neurons and networks. Studying this field has been really suprising and I enjoyed it but having to collect a big ammount of biological biography to understand the model has taken time I would have prefered to use in proofs and mathematical work.

As an overview, one could see that neurons work under an action potential led by internal self mechanisms. This whole process can be expressed as an equivalent circuit. This fact is the first step to mathematical modelling. The first model we studied, Hodgkin and Huxley's, is an accurate and complex model. Due to its difficulty, to study single neurons modeling and the networks modelization, we have taken two easier models: The fist one is the Rubin-Terman model. This model is, as well complex but as it is reduced to a system of two equations, it becomes easier to study. The second one, that is the main focus of this dissertation, is FitzHugh and Nagumo's. They achieved a reduction of Hogdkin-Huxley's model to a much simpler case that under experimentation was defined in a very exact way. This last model is defined by two simple and handy differential equations, which have been studied in this dissertation reaching concepts as the Hopf Bifurcation.

Once studied the models for one single neuron, we have studied the behavior and

modelling of networks, even though before doing so a big research work had to be done to deeply understand the biological theory and how coupling between neurons work.

Finally, in the most important part of my project, I have studied how to create a network of N neurons and I have seen how sensitive the system is under slight changes in its parameters. This section has been studied by numerical calculations with python. The main objective was doing the analytic demostration, simulating what J. Rubin and D. Terman did to their model, applied to the FitzHugh-Nagumo model. The biggest problem I have faced during this thesis, has been running out of time when doing the last and most complex part.

I think that this thesis could be way more extensive, and keep going with different parts of the studies I have made. For example, as equation (5.16) has become complex, I have decided to do a much simpler example to get some results. In my opinion, with more time it would be possible to keep going with the (5.16) and arrive to more specific conditions and properties for the snake. It would also be really interesting to see other kinds of synchrony and doing their study numerically and analitically. In the thesis I have only exposed the one:one synchrony but there are others such as one:two. Another point that I find a possible way to expand this thesis is to see different kinds of networks, for example, those networks with neurons that have different properties, and see how it affects the network. In fact, there are many possible other things to study.

Despite all the difficulties, it has been a really interesting work and I have been able to see how courses such as ODEs Theory have been really useful for this project.

Neuroscience modelling is a really interesting branch of the mathematics, and it could be possible that in a future I get involved in some similar projects.

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Appendix

All the graphics in the Chapter 5, are calculated by *python*. As they all are calculated in a similar way, just changing the number of neurons, the values of the I_{app} and the values of the x-label and y-label, I am only going to post the most complete and complex script which from it, I have taken the last graphics of the network.

There are a few coments during the code where it explains what is done in each step.

```
import numpy as np
import matplotlib.pyplot as plt
from scipy.integrate import odeint
from pylab import *

def sinf(v):
    suma = 0
    for volt in v:
        if volt > alpha:
            suma = suma + 1
        elif volt == alpha:
            suma = suma + 0.5
    return suma

def sistema(var,t):
    v,w,iapp = var[0], var[1], var[2]
    dv = v - (v*v*v)/3. - w + iapp + gsyn * suma * (vsyn - v)
    dw = 0.08*(v + 0.7 - 0.8*w)
    diapp = 0
    return [dv,dw,diapp]

def neurona(x,iapp):
    v = x-(x*x*x/3.)+iapp
```

```
    w = 1.25*x + 0.875
    return v,w

def main():
    global gsyn,vsyn,alpha,suma

    # Constants of the problem
    N = 20
    Imin, Imax = [0.1, 0.35]
    t = np.arange(0,100,0.1);
    dt = np.arange(0,0.11,0.1)
    iapp = np.linspace(Imin,Imax,N)
    inicial_v=np.linspace(-2,-1.5,N);
    inicial_w=np.linspace(1,0,N)
    cont = 0

    #Parameters of synchronization
    gsyn=0.02
    vsyn=0.8
    alpha = 1.5

    #Imax and Imin nullclines
    v_min, w_null = neurona(np.arange(-3.5,3.5,0.01), iapp.min())
    v_max, w_null = neurona(np.arange(-3.5,3.5,0.01), iapp.max())

    #Color of each neuron
    scaled_iapp=(iapp-iapp.min())/(iapp.max()-iapp.min())
    colors = plt.cm.cool(scaled_iapp)

    # Integration for each step dt
    for temps in t:
      cont = 0
      suma = sinf(inicial_v)
      for intensitat in iapp:

        in_var=[inicial_v[cont],inicial_w[cont],intensitat]
        sol = odeint(sistema, in_var, dt)

        #plot the position of each neuron
        plt.plot(sol[1][0],sol[1][1],'*',c=colors[cont],linewidth=2)
```

```
            #the new initial conditions are those obtained in the integration
            inicial_v[cont] = sol[1][0]; inicial_w[cont] = sol[1][1]
            cont = cont+1

        #Imin nullcline
        plt.plot(np.arange(-3.5,3.5,0.01), v_min, c=colors[0])
        #Imax nullcline
        plt.plot(np.arange(-3.5,3.5,0.01), v_max, c=colors[-1])
        #the w nullcline
        plt.plot(np.arange(-3.5,3.5,0.01), w_null, c='b')
        plt.xlim(-3.5,3.5); plt.ylim(-1.5,4)
        plt.title(temps)
        plt.pause(0.1)
        plt.clf()


if __name__ == "__main__":
    main()
```